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Exploring Antiquorum sensing and Antibiofilm potential in Fungi- A Review

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Abstract

Quorum Sensing is a complex microbial interaction involving both extracellular and intracellular signaling between cells that are present in the same matrix to keep track of their physio-chemical processes like formation of biofilm, bioluminescence, siderophore generation, competence, pathogenicity, and many more. Since all these activities are associated with quorum sensing, attenuation/inhibition of quorum sensing activities is a valuable approach to treat pathogenic microbes. Quorum sensing has a parallel role in the generation of multidrug resistance, which highlights the need to search for alternate antimicrobials that disrupt quorum sensing. Apart from the many anti-quorum-sensing compounds derived from plants and bacteria, several compounds originating from fungi have shown the potential to possess antiquorum sensing and anti-biofilm activity. In this review, we have addressed antiquorum sensing and anti-biofilm potential within diverse fungi based on available literature. A thorough understanding of antiquorum sensing and anti-biofilm compounds derived from fungi would undoubtedly help in the creation of efficient therapeutics.

Keywords – Autoinducer molecules – Biofilms – Quorum quenching – Quorum sensing (QS) – Quorum sensing inhibitors (QSIs) – Quorum sensing molecules (QSMs)

Introduction

Diseases by pathogenic bacteria, fungi, parasites, and viruses, greatly impact the morbidity and mortality rates worldwide, especially in developing countries (Livermore 2011). Due to the indiscriminate use of antibiotics, their improper disposal and accumulation in the environment, the past decade has witnessed an increase in multi-drug-resistant pathogenic bacteria and fungi. This is becoming one of the major concerns in the healthcare sector due to a rapid reduction in the antibiotic efficacy against pathogens (Adonizio et al. 2008b, Abinaya & Gayathri 2019). Biofilms are produced by some microbes on reaching an adequate number, which protect them from unfavourable conditions like stress and antibiotics, besides helping them to evade the immune system (Glamočlija et al. 2015). It is proved that treating illnesses caused by biofilm-forming microbes necessitates long-term exposure to medication, which leads to multidrug resistance (MDR) (Singh et al. 2017).

Genesis and subsequent growth of microbial biofilm is regulated by signalling between cells, this phenomenon is known as quorum sensing (QS) (Singh et al. 2017). Quorum Sensing facilitates microbes to determine the density of cells, synchronously govern the gene expression upon

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reaching a threshold called quorum, and simultaneously evaluate the efficiency to produce diffusible extracellular effector molecules (Krzyżek 2019). Apart from biofilm formation, QS mechanisms also control several other mechanisms important for the adaptation and proliferation like bioluminescence, mating, competence, swarming mobility, antibiotic creation, sporulation, toxin production, polysaccharide production, pigment disposition, gene expression, synthesis of exoenzymes, membrane vesicles, siderophores, virulence factors and secondary metabolites with antimicrobial activities (Abinaya & Gayathri 2019, Krzyżek 2019, Mishra et al. 2020, Haque et al. 2020, Joo et al. 2021). To compete with other microorganisms living in close proximity, fungi and bacteria have developed mechanisms such as secretion of secondary metabolites, quorum sensing inhibitors (QSIs), enzymes, and a variety of small molecules. These secondary metabolites, as well as QSIs, inhibit the growth of some microbial communities around them that are present in their milieu (Padder et al. 2018). Among the different sources of QSIs the number of articles on bacterial sources of QSIs are more when compared to plants or fungi, in that order (Fig. 1). In the following paragraphs, we discuss QSIs, anti-quorum sensing (AQS) and anti-biofilm potential in fungal extracts/metabolites.

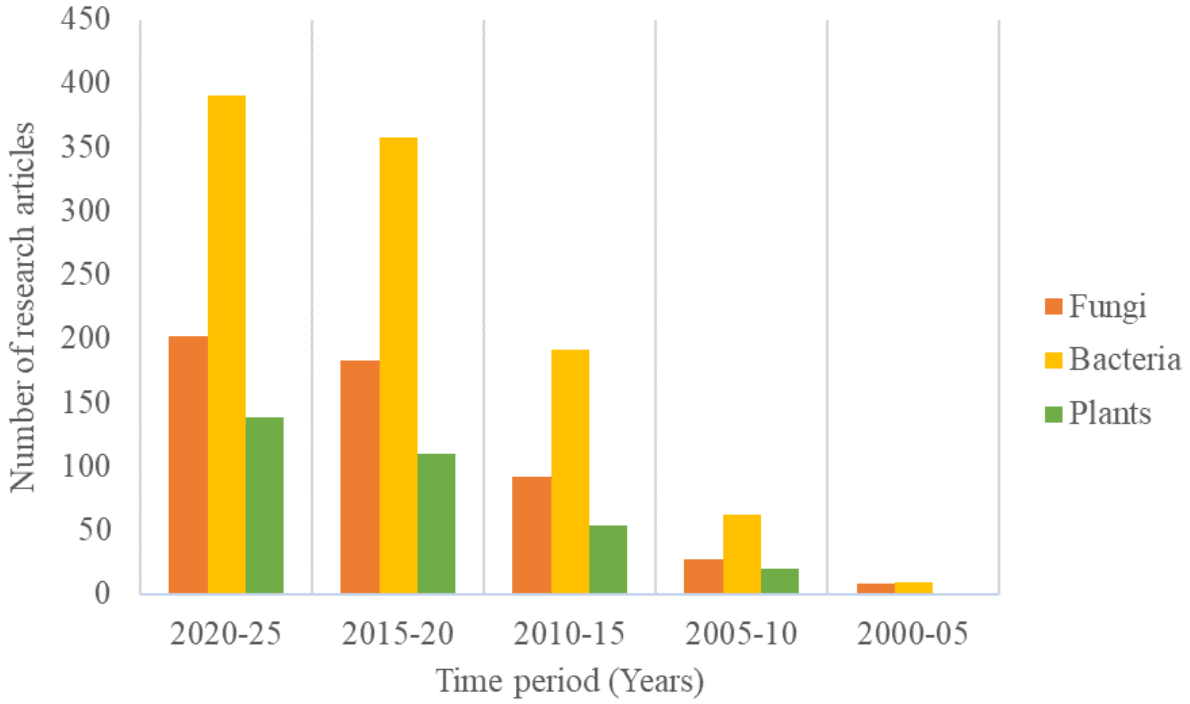

Fig. 1 – Research papers available for anti-quorum sensing compounds from Pubmed.

History of Quorum Sensing

Before 1994, QS was known to be "autoinduction" (Nealson 1977). In 1994, Steven Winans used the term "quorum sensing" in a review paper on autoinduction in bacteria (Haque et al. 2020). This process is linked with the synthesis of extracellular autoinductive molecules with a function comparable to hormones synthesized by higher organisms (Krzyżek 2019). These tiny diffusible autoinductive molecules, generally known as auto-inducers (AIs), play a vital role in cell-to-cell communication mechanisms (Lu et al. 2015). Many major types of small compounds are found to act as autoinducers within microbial QS complexes. For example, autoinducing peptides (AIPs) used by Gram positive bacteria, acyl-homoserine lactones (AHLs) used by Gram negative bacteria and autoinducer-2 (AI-2) used to enable communication between Gram-positive and Gram-

negative bacteria. Thus, QS systems control virulence gene expression in different microbial pathogens (Chang et al. 2021).

About 5 decades ago, various groups of scientists independently discovered autoinducer molecules mediated regulation of bioluminescence in *Vibrio fischeri*, a marine gram-negative bacterium (Haque et al. 2020). QS system was thought to be unique to *V. fischeri*, wherein LuxI-LuxR transcriptional activator and autoinducer system controls the regulation of Lux gene expression based on cell density, which is crucial to produce luminescence (Haque et al. 2020, Padder et al. 2018, Kang et al. 2016). Similarly, *Agrobacterium tumefaciens* uses a LuxI-LuxR-type QS system called TraI-TraR to facilitate the transfer of Ti-plasmid (Lang & Faure 2014). CviI synthase helps in the synthesis of auto-inducer C6-homoserine lactone (C6HSL) in Gram-negative bacterium *Chromobacterium violaceum*. Upon reaching a particular concentration, C6HSL binds to and activates CviR which is a receptor protein. C6HSL-CviR complex stimulates the transcription of vioA to synthesize violacein, a purple pigment that is toxic (Chang et al. 2021). LuxPQ, CqsS, CqsR, and VpsS are four histidine kinase receptors that have been found to control the gene expression in *Vibrio cholerae*. Three QS-AIs, cholera autoinducer-1, autoinducer-2 and DPO [3,5-dimethyl-pyrazin-2-ol] have been reported in *Vibrio cholera* (Mashruwala & Bassler 2020). Gram-positive bacteria, such as *Staphylococcus aureus*, use post translationally modified peptides and AIs to achieve a QS system. The QS system in *Staphylococcus aureus* regulates virulence factor synthesis by cyclic oligopeptides (Younis et al. 2016). The QS system in *Pseudomonas aeruginosa* is a hierarchical structure that contains four interdependent ligand-receptor complexes. These regulatory complexes are LasI/LasR, RhlI/RhlR, PQS, and IQS (Meena et al. 2021). N-butanoyl-homoserine lactone (C4-HSL) and N-3-oxo-dodecanoyl-homoserine lactone (3OC12-HSL) are produced by RhlI and LasI, respectively. With the increase in density of the colony of *Pseudomonas aeruginosa*, C4-HSL and 3OC12-HSL amount also increases and the 3OC12-HSL and C4-HSL binds to the respective genes. This activates some key virulence factors, which in turn accelerate the growth and development of biofilm, by consecutive activation of transcription factors (Haque et al. 2020).

Other functions of quorum sensing molecules (QSMs) include mediating inter-species interactions in microbial communities. The chemotaxis towards AHL signals in marine organisms like the diatoms and the regulation of gene expression in *Burkholderia cepacia* by other bacterial species are some examples (Padder et al. 2018).

Farnesol, a QSM discovered in *Candida albicans*, is a notable development in the QS system in eukaryotes. The discovery of QS in fungi showed that alcohols (1-phenylethanol, farnesol, tryptophol, and tyrosol), acetaldehydes, lipids, peptides, are involved in fungal QS mechanisms, regulating a variety of key activities such as pathogenesis, morphogenesis, filamentation, and so on (Albuquerque & Casadevall 2012, Polke et al. 2015, Hirota et al. 2017, Padder et al. 2018). AIs are sensed by receptors found in organisms' cytoplasm or membranes (Rutherford & Bassler 2012). Almost all auto-inducers, regardless of biochemical nature, behave similarly. Even at smaller concentrations, microbes synthesize these signaling units constitutively. The small signaling molecules/auto-inducers not only diffuse extracellularly but also stockpile in the surrounding environment until it reaches a threshold concentration, at which point they diffuse back to the cell by interacting to the receptor proteins thus starting a differential expression of genes in the microbial population (Abudoleh & Mahasneh 2017, Haque et al. 2020). AIs primarily control the gene expression of a new cell community, thus regulating the microbial reactions (Abinaya & Gayathri 2019). QS regulates gene expression across bacterial communities, allowing microbes to operate as a multicellular entity with advantages over individual microbial cells (Abudoleh & Mahasneh 2017). There are two important scenarios: (i) QS agonists, which mimic AIs as well as focus on promoting non-virulent behaviors, can be used against microbial pathogens that naturally suppress pathogenic traits via QS system, and (ii) QS antagonists, which block microbial interactions, can be utilized against pathogenic microbes that use QS to initiate or sustain virulence (Lu et al. 2015).

Inhibition of QS mechanisms by QSIs-

Different types of antibiotics have been utilized as main anti-infective medications since the early 20th century. However, with the number of untreatable illnesses increasing due to the superbugs, resistance to various antibiotics is becoming a serious concern (Chang et al. 2019, Alfattani et al. 2021). Limited permeability of cellular membranes is the leading cause of antibiotic resistance, which impedes the uptake of effective doses of antimicrobials and increases pathogenicity in the microbial cells (Meena et al. 2020). Anti-quorum sensing (AQS) activity refers to any activity that attenuates QS mechanisms (Mulya & Waturangi 2021). Inhibiting/attenuating QS mediated gene expressions may aid in managing bacterial infections and biofilm formations without harming pathogen's growth or development of microbial resistance against lead compounds/molecules (Kalia 2014, Kalia et al. 2019, Meena et al. 2021, Mulya & Waturangi 2021, Pellissier et al. 2021). Because of this distinct characteristic, pathogenic microorganisms acquire less resistance to QSIs than antibiotics. As QS mechanisms are significant in microbial pathogenesis, drug discovery research and development has focused on the screening of QSIs to tackle microbial infections (Parasuraman et al. 2020a). Several recent studies indicate that various synthetic compounds, natural products, and enzymes with potent antimicrobial properties can quench QS mechanisms or enhance QS signals (Rashmi et al. 2018a, b, Ahmed & Sarma 2020). However, most of the QSIs reported via combinatorial chemistry have proven to be unsuitable for human use, because of their toxicity, limited stability, and poor bioavailability (Silva et al. 2016, Parasuraman et al. 2020a). Consequently, the demand to identify novel QSIs from unexplored natural sources is rapidly growing to achieve an efficient approach for attenuating virulence factors associated with QS and biofilm development.

In recent years, several QSIs of chemical and biological origin have been identified. Among natural sources, compounds from plants such as baicalein, 6-gingerol, zingerone and naringenin from *Scuttellaria baicalensis, Zingiber officinale, Combretum albiflorum* respectively have been observed to have effects on QS regulated virulence in *Pseudomonas aeruginosa PAO1* (Asfour 2018, Vasavi et al. 2017, Parasuraman et al. 2020b). Additionally, microbial secondary metabolites have also been utilized for efficient down-regulation of QS phenomena. Bacteria are widely utilized for developing new secondary metabolites and enzymes for targeting QS mechanisms in pathogenic microbes. Besides bacteria, fungal sources with QS attenuation potential to aim against bacterial virulence have also been observed (Pattnaik et al. 2018, Rashmi et al. 2018a, Ahmed et al. 2020, Mishra et al. 2020). Compounds that inhibit QS mechanisms (aQS compounds) are commonly known as quorum quenchers (QQs) and they are antipathogenic molecules. Different strategies can be employed to disrupt QS systems using AQS compounds: (a) Inhibiting of AIs or synthesis of signalling molecules, (b) Enzymatically degrading QS signalling molecules (c) Inhibiting of signalling molecule/receptor interaction and (d) Utilizing of synthetic inactive analogues of QS signalling molecules (Fig. 2) (Bramhachari et al. 2019, Mondal & Majumdar 2019). Enzymatic degradation of QS diffusible signalling molecules/auto-inducers has shown to be the most beneficial and useful strategy (Pattnaik et al. 2018, Rashmi et al. 2018a, Haque et al. 2020). QS inhibitors (QSIs) or quorum quenchers (QQs) exert less evolutionary pressure on target bacteria for developing resistance since QS is generally not essential for growth. Furthermore, with a few exceptions, QSIs work in a more species-specific manner when compared to antibiotics that kill a broad spectrum of microbes. As QS modulates pathogenesis and virulence in many pathogens, QSIs are called "anti-pathogenic" or "anti-virulence" agents (Joo et al. 2021). The discovery of QSIs has turned out to be a research priority due to the significance of QS (Cruz et al. 2019). In depth understanding about biofilm development and QS are resulting in the discovery of new therapeutic targets to combat pathogenic microorganisms (Petrović et al. 2014). A snapshot of different inhibitory mechanisms of QS by AQS molecules (QSIs) is shown in Fig. 2.

Anti-quorum sensing and anti-biofilm potential in plants and bacteria

In the search for QSIs, research has reported several synthetic and several natural substances having AQS potential with plants being reported as a rich source of such compounds (Meena et al.

2021). Phyto-products obtained from secondary metabolites like flavonoids, terpenoids, alkaloids, and phenolics with oxygen-substituted derivatives (Abinaya & Gayathri 2019). Plant-based compounds have traditionally been used in treating bacterial infections and are considered safe for human ingestion. AQS agents were first characterized in *Delisea pulchra*-a marine alga (Adonizio et al. 2008b). Aqueous extracts extracted from plant sources like *Callistemon viminalis, Bucida buceras, Chamaesyce hypericifolia, Quercus virginiana, Conocarpus erectus and Tetrazygia bicolor* trigger the impediment of genes regulating QS and proteins controlled by it in *Pseudomonas aeruginosa*, with negligible effects on the growth of the bacteria, suggesting that QSI processes aren't related with bacteriostatic and bactericidal effects and they also observed that, *B. Buceras, C. viminalis, and C. erectus* induced considerable biofilm inhibition, pyoverdin production, LasB elastase, and LasA protease production (Adonizio et al. 2008a). Many plants, such as vanilla, clove, and raspberry have been found to contain QSI compound(s) (Rashmi et al. 2018a).

Bioactive compounds found from microorganisms have a variety of activities, including antimicrobial, anti-cancer, anti-malarial, anti-diabetic etc. (Meena et al. 2021). Microorganisms in symbiotic and non-symbiotic relationships with plants produce a diverse spectrum of QSI compounds (Jia et al. 2016). As an alternative to traditional antibiotics, targeting bacteria's QS circuits has been discovered to be a viable approach for combating/counteracting bacterial pathogenesis (Aydemir et al. 2018, Rajkumari et al. 2019). Among bacteria, marine-derived actinomycetes and arctic actinomycetes are a potential source for QSIs (Augustine et al. 2012, Naik et al. 2013). Epiphytic bacteria are observed to be a source of distinct metabolites required for alternative therapies (Abudoleh & Mahasneh, 2017). Actinomycetes have been reported to be potential candidates due to their ability to act as AQS agents for overcoming biofilms formed by food spoilage microbes (Mulya & Waturangi 2021).

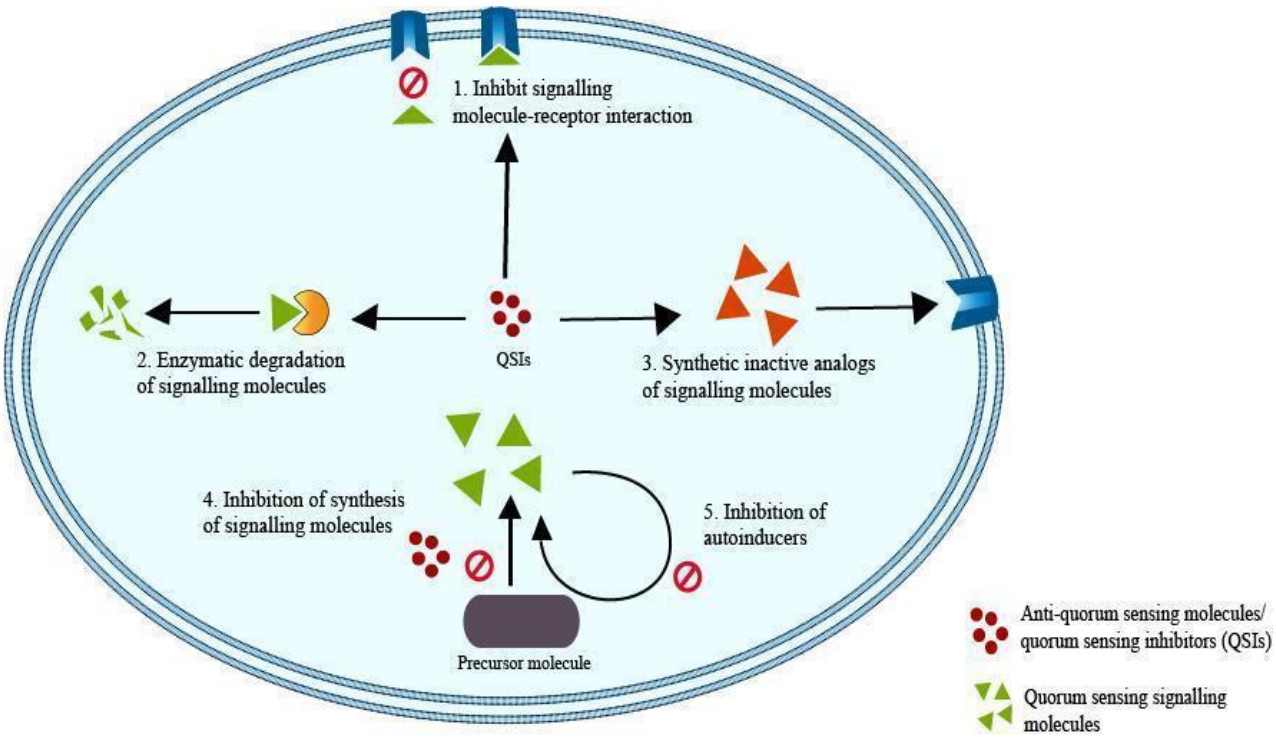

Fig. 2 – Inhibitory mechanisms of quorum sensing by anti-quorum sensing molecules (QSIs).

Antiquorum sensing and Antibiofilm potential in Fungi

QS systems are not just restricted to plants and microorganisms. They have also been observed among fungi (Rashmi et al. 2018a, Mondal & Majumdar 2019). Secondary metabolites associated with fungi have been isolated as significant bioactive metabolites with antifungal,

antiviral, antibacterial, antialgal, antioxidant, anti-proliferative, antimycobacterial, antiplasmodial, immunosuppressive, insecticidal, a-glucosidase inhibitory, cytotoxic, antitumor, and antioxidant activities (Liming et al. 2016, Rashmi et al. 2018b, Chetia et al. 2019, Mondal & Majumdar 2019, Ahmed & Sarma 2020, Meena et al. 2020). The QQ ability of compounds extracted from fungi remain largely untapped, and hence these secondary metabolites might come valuable in producing new anti-pathogenesis compounds (Ahmed & Sarma 2020). It is against this background that the present review on the status of our knowledge on AQS capabilities of compounds/extracts of fungal origin has been undertaken. A table is provided at the end wherein different compounds or extracts of fungal origin that have different kinds of AQS activities against QS bacteria are included (Table 1).

Some fungi cohabit alongside bacteria, since they lack active immune systems, they depend on chemical-compounds for defence. Few of the secondary metabolites are thought to impede the bacterial QS mechanisms (Rasmussen et al. 2005). There have been relatively few recent studies on AQS compounds derived from fungal sources, which poses a challenge in comparing new findings with existing research on fungal extracts. Nonetheless, this indicates that natural and biological products remain the largest repository of compounds for numerous diseases and therapeutic uses (Mishra et al. 2020). Different types of specific fungal-derived compounds have been shown to behave as QSIs against various fungi as well as other prokaryotic bacteria. QSIs must be stable, and resistant to degradation since they have to withstand a variety of metabolic assaults (Padder et al. 2018).

In the following paragraphs the Antiquorum sensing (AQS) activity found in fungi belonging to different ecological niches/groups have been discussed separately.

AQS activities of fungi isolated as endophytes

According to many studies, endophytes produce a broad range of biologically active substances due to their strong biological relationship with their plant host (Chetia et al. 2019). Microbial and plant-derived QSIs are also more favorable than synthetic chemicals owing to their biological character, albeit there has been no observed substantial superiority of microbial endophyte-derived QSIs over plant-derived QSIs. Plant and microbial endophytes synthesize identical phyto-compounds owing to their mutualistic coexistence in the same environment. Thus, plants and endophytes may biosynthesize identical QS inhibitors and may function via the similar inhibitory route (Kusari & Spiteller 2012, Mookherjee et al. 2018). Among the microbial endophytes, numerous important ecological and biotechnological functions are served by fungi (Ferreira et al. 2019). Endophytic fungi populate the interior parts of plants (for example, leaf sheaths, intercellular spaces of aerial plant parts, bark, and root systems) and trade nutrients synthesized with them. Thus, these fungi reduce harmful effects by other microbial pathogens (Rashmi et al. 2018a, Mondal & Majumdar 2019). Endophytic fungi comprise taxa belonging to Ascomycota, Basidiomycota, Zygomycota, and Chytridiomycota that usually live in different environments and synthesize biologically active compounds (Ferreira et al. 2019). They prove to be advantageous and beneficial for industries in increasing the enzyme synthesis along with the synthesis of AQS metabolites (Mondal & Majumdar 2019). These endophytes produce a variety of metabolites, including xanthones, benzopyranones, alkaloids, tannins, flavonoids, phenolic acids, tetralones, chlorinated compounds, steroids, quinones, chinones, terpenoids, saponins etc. (Chetia et al. 2019, Chhipa & Deshmukh 2019).

The crude extracts of foliar endophyte, *Alternaria alternata*, have AQS and antibiofilm activities against *P. aeruginosa* such as a percentage reduction in alginate, pyocyanin, rhamnolipid, and chitinase production; suppression of motility patterns, such as swarming and swimming; a significant decline in proteases activity, such as LasA protease activity, Las B elastase activity and staphylolytic activity; and very noticeable reduction in production of biofilm and factors which are associated to them including exopolysaccharide synthesis (Rashmi et al. 2018b).

Enzyme and AQS compounds produced by endophytic fungi isolated from *Ventilago madraspatana*, using plate assay and spectrophotometric techniques were screened by Rajesh &

Rai (2013). They found a potent protease in *Fusarium sporotrichioides*, QSIs of *F. graminearum* and ethyl acetate extract of a *Lasidiplodia sp*., as indicated by a reduction in violacein pigment production (Rajesh & Rai 2013).

QS activities in *P. aeruginosa* are suppressed by 2,4-di-tert-butylphenol (2,4-DBP) which is extracted from an endophytic-fungi called *Daldinia eschscholtzii*. In a concentration-dependent way, they discovered that 2,4-DBP treatment inhibited production of virulence factor and biofilm along with several related components regulated by QS mechanism. Moreover, 2,4-DBP notably decreased the expression of QS-associated genes, including lasR, rhlR, lasI and rhlI. *P. aeruginosa* adherence was also inhibited by 2,4-DBP in A549 cancer cells. Computational work suggested that 2,4-DBP might bind to the QS receptors LasR and RhlR in pathogen *P. aeruginosa*. Their findings display that 2,4-DBP may serve to address MDR *P. aeruginosa* infections by its anti-biofilm and anti-virulence activity, either as an independent drug or as a combination in different antibiotic treatments(s) (Mishra et al. 2020). Another endophytic fungus, *Phomopsis tersa*, obtained from the leaves of *Carica papaya,* showed QSI activity at sub-Minimum Inhibition Concentration (MIC) level of 900 g/ mL. Pyocyanin and pyoverdin pigments were inhibited at 92.5 % and 71.5%, respectively by the aqueous extracts of *P. tersa.* It also inhibited virulence factors expression that assist construction of biofilm like exopolysaccharides, alginates by 72.21% and 72.50%, respectively. Enzymes capable of lysing cells were also reduced: chitinase secretion was lowered by 79.73%, while elastase secretion was reduced by 74.30%. GC-MS study revealed that 3-isobutylhexahydropyrrolo [1,2-a] pyrazine-1,4-dione could interact efficiently with LasR and RhlR of *P. aeruginosa* pathogen. Bioactive molecules found in their research might be used as novel drug candidates to combat chronic infections (Meena et al. 2020).

Lasiodiplodia pseudotheobromae IBRL OS-64, is an endophytic fungus, which showed anti-biofilm efficacy from its ethyl-acetate extract against the food borne bacteria, *Yersinia enterocolitica*. The initial biofilm of the pathogen was more susceptible than the preformed biofilm. The fungal extract markedly reduced extracellular polysaccharide (EPS) matrices and inhibited the attachment of bacterial cells in biofilm development. They concluded that the extracts of *L. pseudotheobromae* IBRL OS-64 could be used as efficient anti-biofilm and antibacterial agents to combat foodborne infections (Taufiq & Darah 2020).

Lasiodiplodia venezuelensis thriving endophytically in *Astrocaryum sciophilum* leaves has shown AQS activities against *P. aeruginosa* and is found to produce eight compounds including two pyran-derivative compounds that can target various *P. aeruginosa* QS systems (Pellissier et al. 2021). These compounds strongly inhibited the synthesis of some essential virulence components, while also reducing the expression of genes lasB and rhlA without hindering the growth of *P. aeruginosa* (Pellissier et al. 2021). Leaves of *Carica papaya* hosting *Colletotrichum gloeosporioides* HM3, was examined by Meena et al. (2021) and at a concentration of 750 µg/ml, the crude extract showed bacteriostatic impact on *P. aeruginosa* PAO1. They found that it highly reduced the production of virulence factors controlled by QS such as chitinase, elastase enzyme, and pyocyanin by 56.32%, 62.54 %, and 66.67%, respectively and a reduction in EPS, rhamnolipid, and HCN production. They also found inhibition of bacterial ability to build complex biofilm architecture through light microscopy and CLSM analyses (Meena et al. 2021).

AQS activities of fungi from marine environments

Aspergillus flavipes AIL8, an endophytic fungus found to colonize the inner leaves of *Acanthus ilicifolius*, synthesizes a novel aromatic butyrolactone chemical called Flavipesins A (Bai et al. 2014). This compound has shown remarkable antibacterial action against *Staphylococcus aureus* and *Bacillus subtilis* at MICs 8.0 µg/mL and 0.25 µg/mL, respectively, in addition to an antibiofilm activity by reducing the live cells embedded in the biofilm matrix (390.6 to 97.7 µg/mL). The study suggests that flavipesins A might kill live cells inside the grown *S. aureus* biofilm by penetrating the biofilm matrix (Bai et al. 2014). It has been shown that polyhydroxyanthraquinones, the organic compounds from the fungal endophyte *Penicillium restrictum*, produce QSIs that have anti-virulence ability against a clinical bacterial isolate of

methicillin-resistant *Staphylococcus aureus* (MRSA) (IC50 ranges from 8 to 120 μM (Figueroa et al. 2014). *Phomopsis liquidambari,* an endophytic fungus was reported to have potent AQS molecule 1-(4-Amino-2-hydroxyphenyl) ethenone, which downregulates the expression of LasI and RhII by competitively inhibiting QS- related receptors in *P. aeruginosa* (Zhou et al. 2021).

Marine algicolous *Arthrinium* spp. has been reported to have cellulolytic, radical-scavenging and antifungal properties (Heo et al. 2018). They inhibit QS activity by generating QSIs such as bentonicine, isoethionic, and floridoside acid from *Ahnfeltiopsis flabelliformi* (a Korean red alga) and bromoperoxidase from *Laminaria digitate* (a brown alga). Heo et al. (2018) reported that *Arthrinium sp*. extracts interfered with violacein production by *C. violaceum* CV026 when exposed to N-(3-oxo-hexanoyl)-L-homoserine lactone (3-oxo-C6-HSL), an extensively used QSM (Heo et al. 2018). AQS and antibiofilm properties against *P. aeruginosa* PAO1 were shown in a metabolite equisetin produced by a marine isolate of *Fusarium sp.* Z10, which prevents the development of biofilm, virulence factors synthesis, and swarming motility (Zhang et al. 2018b).

Pestalotiopsis sydowiana PPR is a marine fungus, and its extract has been reported to contain effective AQS properties against *P. aeruginosa* (Parasuraman et al. 2020a). It also inhibits motility and some of its virulence characteristics along with reduction in development of biofilm. The impediment of QS-regulated virulence characteristics such as the pyocyanin, chitinase enzyme, protease, staphylolytic and elastase activities were 84.15%, 73.15%, 67.37%, 33.65%, and 62.37%, respectively. Furthermore, it caused a reduction in the production of EPS, rhamnolipids, and alginate by 74.99%, 68.01% and 54.98% respectively. It also hindered the development of bacterial biofilms by 90.54%. Amongst *P. sydowiana* PPR extracts, CLP and 4-HPA, showed efficient prevention of the production of virulence genes regulated virulence genes regulated by QS along with biofilm formation and growth in *P. aeruginosa* PAO1. MIC values of CLP and 4-HPA against *P. aeruginosa* PAO1 were 250 and 125 g/ml, respectively. Their molecular docking and molecular dynamics (MD) simulations collectively predicted a highly efficient interaction between fungal metabolites and bacterial QS receptors. Thus, the study reports that CLP and 4-HPA downregulate production of various virulence factors associated with QS in *P. aeruginosa* PAO1 without hindering its growth. Their findings suggested that *P. sydowiana* PPR metabolites might be able to disrupt the QS system while also reducing pathogenicity of *P. aeruginosa* PAO1 (Parasuraman et al. 2020a).

Tyrosol, an active molecule produced by a marine isolate of *Penicillium chrysogenum* DXY-1, was reported to have AQS activity. In *C. violaceum* at 0.5mg/mL violacein production was reduced by 53.5%. In *P. aeruginosa* PA01 a reduction by 63.3%, 57.8% and 9.9% respectively was observed for pyocyanin production, elastase and proteolytic activity. Results from SEM displayed biofilm inhibition takes place without any effect on bacterial growth when treated by tyrosol. Molecular docking of C6HSL (a natural signal molecule) and tyrosol showed that they bind to CviR-a receptor pocket, whereas tyrosol inhibited CviR QS action in *C. violaceum* by interacting with the DNA binding domain and preventing expression of virulence genes. The study shows the potential of the new molecule tyrosol as an inhibitor of QS mechanism to combat the pathogenic bacterial resistance (Chang et al. 2019).

Metabolites of *Blastobotrys parvus* PPR3, isolated from *Avicennia* sp. in mangroves, interacting with the QS system of pathogen *P. aeruginosa* PAO1 by modifying the synthesis of virulence factors was shown by Parasuraman et al. 2020b. In biosensor strain, *Chromobacterium violaceum*, and test bacterium *Pseudomonas aeruginosa* PAO1, the crude extracts of *Blastobotrys parvus* PPR3 at various sub-MIC concentrations, reduced the synthesis of elastase enzyme, chitinase enzyme, protease enzyme, pyocyanin, swimming and swarming motility, biofilm formation, production of exopolysaccharide and alginate in *P. aeruginosa* PAO1 (Parasuraman et al. 2020b). *Fusarium petroliphilum,* isolated from *Posidonia oceanic* a Mediterranean seagrass, showed antibacterial properties with its ethyl extracts against methicillin-resistant *S. aureus* whereas it has no activity against *P. aeruginosa*. Reporter assay identified the QS inhibitory activity of the crude fungal extract against pathogen *P. aeruginosa* (Alfattani et al. 2021).

Only few reports of AQS activities by marine fungi are reported and those are mainly based on the marine-derived and/or facultative marine fungi and not from typical marine fungi. This is an area for future studies.

AQS activities of edible mushrooms

Researchers investigated the AQS and antibiofilm activities from *Inonotus obliquus* (Chaga mushroom) crude extracts on *P. aeruginosa* PAO1 and found a decrease in twitching and swarming as well as the quantity of pyocyanin synthesized as QS metrics (Glamočlija et al. 2015). It was reported that extracts of *Armillaria mellea* (honey mushroom) hinder QS controlled processes including biofilm development, pyocyanin synthesis (reduced by 38.47%) and motility of *P. aeruginosa* (Kostić et al. 2017).

Tremella fuciformis, belonging to the basidiomycetes also called the white jelly mushroom; it is a gourmet cuisine/food and a medicinal fungus popular among Chinese people. Despite its widespread usage, *T. fuciformis* has received little attention in terms of antibacterial action. It has been shown that the extracts of *T. fuciformis* could prevent QS-regulated behaviors by quantifying the reduction in the violacein pigment synthesis as an indicator of QS inhibitory activity (Zhu & Sun 2008). Zhu et al. (2011) reported a similar ability in a jelly fungus *Auricularia auricular*, which had inhibited violacein pigment production in *C. violaceum* which is QS regulated while leaving its growth and development unaffected (Zhu et al. 2011).

QSIs which were enzyme based was reported from a basidiomycete, *Trichosporon loubieri*. These QSIs break down various AHLs which may/may not have substitution of oxo group at C3 of the various N-acyl side chains, through the action of lactonase enzyme (Wong et al. 2013, Padder et al. 2018). The edible fungus *Agaricus blazei* has been reported to be having immunomodulatory properties that protect against a number of infectious disorders in addition to significant AQS abilities. Extracts of *A. blazei drastically* reduced the pyocyanin production, swimming motility, and twitching at sub-MIC concentrations which neither killed nor hindered the bacterial growth. Further, the biofilm forming ability was inhibited in a concentration-dependent manner (Sokovic et al. 2014). *Agrocybe aegerita*, which is a popular nutritious edible mushroom, has been shown to be having antioxidant, antibacterial, and AQS activities against *P. aeruginosa*. Methanolic extracts of *A. aegerita* have controlled the expression of virulence factors like swimming motility, twitching, pyocyanin synthesis and biofilm development in *P. aeruginosa* dose dependently. *A. aegerita* extracts can thus be an excellent source for such bioactive compounds (Petrović et al. 2014).

AQS activities of endolichenic fungi (ELF)

In the quest for novel bioactive compounds of pharmaceutical importance, endolichenic fungi (ELF) provide prospective sources of unique natural products, particularly for anticancer and antifungal medication (Lagarde et al. 2019). Endolichenic fungi (ELF) have emerged as potential natural sources in recent years owing to their ability to synthesize new pharmacological compounds (Prateeksha et al. 2020). Antibiofilm action against *Candida albicans* by compounds from endolichenic fungi like pyridoxatin, biatriosporin D, floricolin produced by *Tolypocladium cylindrosporum*, *Biatriospora sp.*, and *Floricola striata* respectively have been reported (Chang et al. 2015, Zhang et al. 2017, 2018a). It was reported that the antibiofilm and antiproliferative capabilities of crude extracts of endolichenic fungi such as *Daldinia, Nemania, Coniochaeta,* and *Peziza* associated with the lichen *N. laevigatum*, can hinder the *C. albicans* biofilm development (Lagarde et al. 2019).

The QS and biofilm formation in *P. aeruginosa* PAO1 were prevented by an endolichenic fungal strain, *Aspergillus quandricinctus*, at 4 mg/ml conc. of crude extracts, without impacting the growth and survival of the bacterium, in a concentration-dependent manner, along with the reduced production of virulence factors like protease, pyocyanin, rhamnolipids, elastase, and EPS in *P. aeruginosa* PAO1 (Prateeksha et al. 2020).

AQS activity in leaf litter degrading fungi

Quorum quenching potential was reported from the crude extracts of *Phomamultirostrata* PUTY3, a saprophytic fungus isolated from *Carica papaya,* against *Pseudomonas aeruginosa* by reducing the synthesis of virulence factors namely pyocyanin, rhamnolipids, elastase, HCN gas generation, protease, along with biofilm (Ahmed & Sarma 2020). Additionally, a considerable suppression of motility characteristics like swimming, twitching and swarming in *P. aeruginosa* was reported. According to their *in-silico* study, the chemical contained in the *P. multirostrata* extract, 1,1-Dichloro-2- Methyl- 3- (4, 4- Diformyl- 1, 3- Butadien- 1- yl) Cyclopropane, is efficiently binding with LasR which is a receptor protein, while the 1,2 Benzenedicarboxylic acid, Bis (2- Methylpropyl) Ester, interacts with receptor RhlR, inhibiting the QS mechanism in *P. aeruginosa*. These results revealed novel anti-infective and alternative therapeutic strategies that can be used to counteract *P. aeruginosa* and emphasized the need to explore fungal derivatives from different saprophytic fungi inhabiting decaying plant substrates (possessing therapeutic properties) (Ahmed & Sarma 2020).

Ahmed et al. (2020) have shown that secondary metabolites from *Mycoleptodiscus indicus* PUTY1 exhibited QQ ability, indicating a novel alternative strategy for countering *P. aeruginosa* pathogenicity by interfering with LasR and RhlR receptor proteins. The *in vitro* results included decrease in virulence factors (pyocyanin, elastase, protease, rhamnolipids, HCN gas, EPS), motility (swarming, swimming, twitching) and biofilm generation. I*n silico* of GC-MS-detected compounds of *Mycoleptodiscus indicus* using LasR and RhlR proteins further verified the *in vitro* findings (Ahmed et al. 2020).

AQS activity in fungi from soil and other environments.

A screening of some strains of *Penicillium* spp. to produce QSI activity showed that several extracts produced QS inhibitory chemicals (Rasmussen et al. 2005). Amongst all the extracts almost 33% of them were reported to have characteristics to be potential QSIs. Further investigation of *Penicillium radicicola* and *Penicillium coprobium* revealed the QSI produced to be penicillic acid and patulin respectively. DNA microarray transcriptomics was used to validate the effects of patulin and penicillic on the gene expression regulated by QS (Rasmussen et al. 2005).

In producer microbes, different categories of biosurfactants have different characteristics and possess a broad range of actions, like microbial pathogenesis, higher solubilisation of compounds hydrophobic in nature, binding of heavy metals, and so on. Biosurfactants have also been identified to prevent harmful organisms from adhering to infection sites or solid surfaces, inhibiting biofilm development, which leads to many disorders like cystic fibrosis. Thus, prior attachment of biosurfactants to solid surfaces could offer a novel and efficient strategy in preventing colonization of harmful microbes and biofilm development. Researchers found that the novel biosurfactant derived from *Candida sphaerica* had antibacterial and antiadhesive effects against numerous pathogenic and non-pathogenic microbes. The biosurfactant's critical micelle concentration (CMC) was estimated at 0.25 mg/ml^{-1} and surface tension measured at 25 mN/m. Antiadhesive and antibiotic activities of the biosurfactant were tested against a range of microbes at various concentrations (0.625-10 mg/ml^{-}). Biosurfactant at the greatest dose, which was tested, exhibited antibacterial efficacy against *Candida albicans*, *Staphylococcus epidermidis*, and *Streptococcus oralis* at 57%, 57.6%, and 68% respectively. Also, at 10 mg/ml concentration of the biosurfactant, the adherence of *Streptococcus agalactiae*, *Streptococcus sanguis* and *Pseudomonas aeruginosa* reduced by 80 to 92 %. Their findings suggest that this biosurfactant could be used in the medical field as an alternative antimicrobial agent against microbes that cause serious infections and diseases in the gastrointestinal tracts, vaginal, and urinary, and on the skin. Moreover, its antiadhesive properties might make biosurfactants a suitable protective layer for different medical devices (Luna et al. 2011).

Chrysin, an ethyl acetate extract derived from *P. chrysogenum* DXY-1, displayed AQS activity. A 20 μg/mL dosage of chrysin decreased violacein pigment synthesis controlled by QS in *C. violaceum* CV026 by 31.6 %. When the dosage was doubled, it reduced various QS related

enzyme activity like elastase, pyocyanin, proteolytic enzyme activity, and biofilm development in *P. aeruginosa* PA01 by 13.8 %, 41.4%, 8.3 %, and 42.4%, respectively and chrysin also seem to prevent *P. aeruginosa* PA01's swarming activity. Their molecular docking studies indicated that chrysin competes with C6HSL to bind to the same site of the CviR receptor thereby inhibiting the QS system. On the other hand, their CD (circular dichroism) findings showed that chrysin might alter CviR's secondary structure, preventing 'C6HSL/CviR binding' and suppressing the bacterial QS mechanism (Chang et al. 2021). Yu et al. (2021) reported an AQS molecule Cyclo (L-Tyr-LPro) produced by *Penicillium chrysogenum* DXY-1 to competitively bind with receptors and inhibit QS autoinducers in *C. violaceum* CV026 and *P. aeruginosa* PA01 (Yu et al. 2021).

These studies indicate that different molecules/compounds/enzymes originating from fungal sources have a hidden potential to break down the QSMs also preventing biofilm formation (Padder et al. 2018, Wong et al. 2013).

Table 1 Anti-quorum sensing compounds from fungi.

Sr. no.	Mode of action	Fungal species	Target organism	Compound reported	Anti-QS target	References
1.	Inhibit signalling molecule-receptor interaction	*Aspergillus terrus*	*C. violaceum, Agrobacterium tumefaciens*	Terrein	Blocking QS receptors	Kim et al. 2018, Tilvi et al. 2022
		Phomopsis liquidambari	*Pseudomonas aeruginosa*	1-(4-Amino-2-hydroxyphenyl) ethanone	Competitive inhibition of QS-related receptors	Zhou et al. 2021
		Alternaria alternata	*Pseudomonas aeruginosa*	Sulfurous acid, 2-propyl tridecyl ester	Inhibition of LasR	Rashmi et al. 2018b
		Penicillium chrysogenum DXY-1	*C. violaceum* CV026 and *P. aeruginosa* PA01	Tyrosol	Binding to DNA binding domain of the CviR receptor pockets	Chang et al. 2019
		Phoma multirostrata PUTY3	*Pseudomonas aeruginosa*	1,1-Dichloro-2-Methyl- 3- (4, 4-Diformyl- 1, 3-Butadien- 1- yl) Cyclopropane,	Binding to the LasR receptor protein	Ahmed & Sarma 2020
		Phoma multirostrata PUTY3	*Pseudomonas aeruginosa*	1,2 Benzenedicarboxylic acid, Bis (2-Methylpropyl) Ester	Interaction with the RhlR receptor protein	Ahmed & Sarma 2020
		Pestalotiopsis sydowiana PPR	*Pseudomonas aeruginosa* PAO1	CLP and 4-HPA	Interaction with bacterium's QS receptor proteins (LasR and RhlR)	Parasuraman et al. 2020a

Table 1 Continued

Sr. no.	Mode of action	Fungal species	Target organism	Compound reported	Anti-QS target	References
		Daldinia eschscholtzii	*Pseudomonas aeruginosa*	2,4-di-tert-butylphenol (2,4-DBP)	Binding to LasR and RhlR receptors	Mishra et al. 2020
		Mycoleptodiscus indicus PUTY1	*Pseudomonas aeruginosa*	Phenol, 2,4-bis(1,1-dimethylethyl) and 1,2 benzenedicarboxylic acid, bis(2-methylpropyl) ester	Competitive binding to protein receptors LasR and RhlR	Ahmed et al. 2020
		Penicillium chrysogenum DXY-1	*C. violaceum* CV026	Chrysin	Competitive binding with a natural signaling molecule C6HSL, for the same pocket of the CviR receptor Altering secondary structure of CviR and preventing C6HSL/CviR binding	Chang et al. 2021
		Penicillium chrysogenum DXY-1	*Chromobacterium violaceum* CV026 and *Pseudomonas aeruginosa* PA01	Cyclo(L-Tyr-LPro)	Competitive binding with receptor proteins	Yu et al. 2021
		Blastobotrys parvus PPR3	*Pseudomonas aeruginosa* PAO1	Ethyl acetate extract having compounds - 2- Phenylethanol, Phenylacetic acid, 2-(4-Hydroxyphenyl) ethanol, 2-Hydroxyphenylacetic acid, 2,4-Di-Tert-butylphenol and Phenylalanylprolyl diketopiperazine	Interaction with LasR and RhlR receptors	Parasuraman et al. 2020b
2.	Enzymatic degradation of signalling molecules	*Trichosporon loubieri*	-	-	Degradation of AHL signalling molecules having *N*-acyl side chains	Wong et al. 2013

Table 1 Continued

Sr. no.	Mode of action	Fungal species	Target organism	Compound reported	Anti-QS target	References
3.	Inhibition of synthesis of signalling molecules	*Penicillium radicicola*	*Pseudomonas aeruginosa*	Penicillic acid	Affected QS regulated genes at post transcriptional level, preferentially targeting RhlR- and LasR controlled genes	Rasmussen et al. (2005)
		Aspergillus terrus	*Pseudomonas aeruginosa*	Terrein	Inhibiting the production of QS signaling molecules	
4.	Inhibition of autoinducers	*Penicillium radicicola*	*Pseudomonas aeruginosa*	Penicillic acid	Affected QS regulated genes at post transcriptional level, preferentially targeting RhlR- and LasR controlled genes	Rasmussen et al. (2005)
		Penicillium. coprobium	*Pseudomonas aeruginosa*	Patulin	Affected the expression of QS regulated genes at post transcriptional level with high specificity of RhlR- and LasR controlled genes	Rasmussen et al. 2005
		Fusarium sp. Z10	*Pseudomonas aeruginosa* PAO1	Equisetin	Inhibition of las, rhl, PQS QS systems	Zhang et al. 2018b
		Daldinia eschscholtzii	*Pseudomonas aeruginosa*	2,4-di-tert-butylphenol (2,4-DBP)	Downregulating QS related gene expression (lasI, lasR, rhlI, and rhlR)	Mishra et al. 2020
		Phomopsis. tersa	*Pseudomonas aeruginosa* PAO1	3-isobutylhexahydropyrrolo[1,2-a] pyrazine-1,4-dione	Interaction with transcriptional controllers LasR and RhlR	Meena et al. 2020

Table 1 Continued

Sr. no.	Mode of action	Fungal species	Target organism	Compound reported	Anti-QS target	References
5.	Unknown mechanism	*Tremella fuciformis*	*C. violaceum*	Crude extract	-	Zhu & Sun 2008
		Auricularia auricular	*C. violaceum*	Crude extract	-	Zhu et al. 2011
		Fusarium graminearum	*C. violaceum* C026	Crude extract	-	Rajesh & Rai 2013
		Agaricus blazei	*Pseudomonas aeruginosa* PAO1	Water extract	-	Sokovic et al. 2014
		Agrocybe aegerita	*Pseudomonas aeruginosa*	Extract rich in phenolic compounds	-	Petrović et al. 2014, Bains et al. 2023
		Penicillium restrictum	Methicillin-resistant *Staphylococcus aureus*	Polyhydroxyanthraquinones	-	Figueroa et al. 2014
		Inonotus obliquus	*Pseudomonas aeruginosa* PAO1	Ethanolic and aqueous extracts	-	Glamočlija et al. 2015
		Armillaria mellea	*Pseudomonas aeruginosa*	Methanolic extract	-	Kostić et al. 2017
		Arthrinium spp.	*C. violaceum* CV026	-	-	Heo et al. 2018
		Aspergillus quandricinctus	*Pseudomonas aeruginosa* PAO1	Crude extract	-	Prateeksha et al. 2020
		Lasiodiplodia venezuelensis	*Pseudomonas aeruginosa*	Two pyran-derivative compounds	Targets QS regulated genes lasB and rhlA	Pellissier et al. 2021
		Fusarium petroliphilum	*P. aeruginosa and S. aureus*	Crude extract	-	Alfattani et al. 2021

Conclusion & Future Prospects

Inhibition of microbial QS systems brings a new hope in challenging MDR microbes when compared to bactericidal or bacteriostatic approaches, because QS is not directly involved in microbial growth or development nor does it provide any selection pressure on the development of resistance as antibiotics do (Zhu & Sun 2008, Pattnaik et al. 2018).

However, the production of QSIs calls for further research on the mode of action of QSIs and their cellular toxicity (Bramhachari et al. 2019). Research focusing on the pathogen's pathogenicity and behavior in infections is necessary to design effective QSIs to tackle different microbial diseases. Despite the encouraging laboratory findings, it is apparent that we lack a complete understanding on how QS inhibition affects pathogen fitness under more compelling circumstances, including diverse microbial communities, external environment, and host interactions (Mishra et al. 2020). Hence, these aspects should be extensively explored before any QSI is approved and placed in the market (Bramhachari et al. 2019).

The studies on anti-QS and anti-biofilm compounds/extracts derived from fungal sources are of recent in origin and are few and the same makes it incomplete to compare with other bacterial sources. Further, most of the studies on bioactive compounds/molecules/inhibitors from fungi having anti-QS and anti-biofilm activities have been tested against only the MDR pathogen *P. aeruginosa* and reporter strain *C. violaceum*. We need to expand the horizon and test the QSIs produced by fungi against other pathogenic microbes that form QS and biofilms, in future, to control other pathogenic microbial infections also. Designing bioprocess technology for natural QSIs, particularly from fungi, on an industrial scale, is an area that needs to be explored in future through further studies, development and discoveries (Mookherjee et al. 2018). The present review shows that there are only a few studies on AQS potential studied from fungal sources. More fungal strains and cultures from varied environments need to be studied and explored in future.

Conflict of Interest: "Declarations of Interest: none"

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