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A WAY OF COMBATING ANTIMICROBIAL RESISTANCE THROUGH QUORUM SENSING

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ABSTRACT: Quorum sensing is a peculiar mechanism of microbial communication through the induction of various signalling autoinducer molecules having several gene expression regulatory activities of different virulence factors that control microbial. This enables a systematic path of inhibiting microbial growth and its infection production efficacy by indirectly regulating the Quorum sensing activity of the concerned pathogens. As antimicrobial resistance directly impacts the healthcare system, hence is one of the biggest threats to global health. The attenuation or inactivation of these resistant variety bacteria is the utmost call of hour. In this panorama, interference/change in the chemical signal of QS system has been developed as an efficient technique to block their expression, hence enabling them as less virulent. A literature study was performed using online research, including database searches such as PubMed, SciELO, and SCOPUS between 2000-2020. This review aims to provide a brief mechanism of inhibition of microbial resistance through QS system by different strategies.

INTRODUCTION: The breakthrough insight for the generation of neo-antibiotics and their ruthless utilization led to a major crisis in the human world; where the pathogenic microbes have developed resistance against more and/or all the available antibiotics leading to the development of multi-drug resistant (MDR) strains of pathogens [1, 2]. To inhibit or regulate their growth, several physiological processes have been adopted that kill the pathogen by destroying its protein bio-synthesis mechanism or disrupting its membrane structures. However, the increased use of antibiotics indirectly helps the microbes generate resistant pathogenic varieties [3] that cause severe health havoc in today's healthcare system [4].

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Three vital techniques have developed the resistant efficacy of microbes, *viz.* chemical modification of antibiotics by secretion of certain alternative enzymes to degrade the concerning antibiotics and attenuate its efficacy by scattering the functional groups [5], efflux pump (lipophilic and/or hydrophilic efflux pump) activation by microbes on the cell membrane that systematically removes desired antibiotics, which is done by higher excretion rate compared to the drug penetration rate to regulate the concentration of the antibiotics as minimum as possible [6] and alternation in the drug-targeting genes by modification of targeted gene or interference with the targeted site so that the antibiotic target will be lost [7].

In pathogenic microbes, especially in bacteria, some kind of extracellular chemical signalling molecules, called auto-inductors are being secreted that interact with the receptor protein leading to coordinated changes in the expression of specific genes to counteract the activities of antibiotics [8]. Precisely Quorum sensing (QS) is a mechanism

that enables microbial interaction based on the secretion of auto inductors to the environment [9]. This developed mechanism of bacteria has machinated complex tools to inhibit the disruption of concerned microbes leading to the increased population of MDR strains, as it mostly regulates maximum cellular metabolic functions of microorganisms, including pathogenic gene expression, toxin production and elevating drug efflux system and microbial biofilms formation [10].

Bacterial efflux pump systems that effectively drop off antibiotics into the bacteria are mostly regulated by QS systems [11, 12]. The QS regulation mechanism involves both up-regulations of MDR pump MexAB-OprM, causing the development of MDR bacterial strain [13] along with some impact on the QS system itself [14]. As bacterial biofilms have a direct relation with their resistance, regulation of bacterial biofilm formation by QS can directly affect the resistance efficacy of the concerned microbe [15], achieved by incurring nutrition restriction [16] and drug resistance phenotypic methods [17]. Pathogenic bacteria secrete certain proteins as toxins that kill other microbes and damage the host immune system, which is transported by several secretory systems [18]. The regulation of these secretory systems can prevent the resistant efficacy of the concerned bacteria. The type I secretion system (T1SS), present in Gram-negative bacteria, is regulated by the Has system of *Serratia marcescens* and *Pseudomonas aeruginosa*, and the hemolysin system of *Vibrio cholerae*, *Neisseria meningitidis* and *E. coli* [19]. Similarly, the type II secretion system (T2SS), present in Gram-negative bacteria, is regulated by Xcp system of *P. aeruginosa* [20]. As the QS system plays a pivotal role in inhibiting bacterial-resistant variety development, the resistant efficacy of that microbe can be suppressed by interfering with the QS system of the desired microbe. However, in this meta-analysis, a brief comparative study regarding the different QS system inhibition strategies has been elaborately described.

MATERIALS AND METHODS:

Source: For the process of meta-analysis at the initial stage, three major research databases, namely SCOPUS, PubMed, Science Direct were searched in order to collect related articles. However, almost all the articles found in the PubMed and Science Direct databases were available in the Scopus database as well, and therefore SCOPUS database was used as the source for the collection of primary data for the review. The articles were selected from the database using relevant keywords like “Quorum sensing”, “Microbial resistance”, “Quorum quenching”, “Regulation of Bacterial Efflux Pump by QS”, “Regulation of Bacterial Biofilm Formation by QS”, “Regulation of Bacterial Secretion System by QS” *etc*. These collected research papers were inspected thoroughly for further analysis.

Data Extraction: After identifying the core theme, the papers selected under the themes were subjected to extensive reading. To prevent bias in the selection of papers, “The Preferred Reporting Items for Systematic Review and Meta-Analysis” (PRISMA) flow chart has then been prepared to demarcate the inclusion and exclusion criteria for the selected papers. The SCOPUS database was also used to obtain various bibliometric trends which were used to analyze various perceptive of research contributions under the selected research topic.

RESULT & DISCUSSION: The excessive use of antimicrobial drugs has paved the path for the microbes to generate and sustain the generalized threat and helps in adopting, to be more précised, creating the multidrug-resistant (MDR) strains. This creates a major threat to mankind as most of the present drugs remain inactivated for treating them [21]. To solve this issue, regulation of Quorum sensing (QS) Signalling molecules can play a vital role as it has direct control over all the virulent factors of the microbe within the host body. The regulation of QS-secreted auto inductors not only means inhibition of concerned molecules; however, this can also be achieved by degradation of signal molecules or inhibiting signal molecule conduction to the specific receptors [22]. For this reason, excessive studies have been going on regulating the QS activity of microbes, thus controlling the infections caused by resistant strains. For the data extraction, the selected papers' key data were screened and analyzed on the following set of particulars: details of the authors with a year of publication, Test Organism; Strategy Mechanism; and Biological Effects.

These key data sets were summarized in the following table to ease further theme-wise analysis **Table 1.** Quorum sensing is an efficient mechanism that regulates the communal behaviour of microbes, mostly by controlling specific gene expression. In most microbial physiological pathways, such as exopolysaccharide and toxin production, biofilm formation is generally influenced by quorum sensing. However, quorum-sensing-interfering (QSI) compounds synthesized naturally and/or artificially have both positive and negative impacts on the microbial signalling network [23].

TABLE 1: INHIBITION STRATEGIES OF QS SYSTEM

Sl no.	Author	Test Organism		Strategy Mechanism	Biological Effects
1	[24]	*Escherichia coli*	Inhibition of signal molecule production	Methylthio-DADMeimmucillin-A, downregulates 5'-methylthioadenosine and hydrolyzesS-adenosyl-homocysteine nucleosidase	Inhibition of methylation, polyamine synthesis, methionine salvage and QS pathways
2	[25]	*Vibrio cholera*		Picomolar inhibitor, MT-DADMe-ImmA synthesized through 5′-methylthioadenosine phosphorylase (MTAP) blocks QS in *Vibrio cholerae* without affecting the growth rate	Inhibition of QS signal AI-2
3	[26]	*Vibrio Harvey* BB170		Synthetic peptide TNRHNPHHLHHV showed a specific inhibitory effect on LuxS enzyme activity	Inhibition of QS signal AI-2
4	[27]	Pathogen		Brominated furanone inactivates LuxS enzyme that produces autoinducer-2 (AI-2)	Inhibition of QS signal AI-2
5	[28]	*E. coli*		5'-Methylthioadenosine/S-adenosylhomocysteine nucleosidase (MTAN) regulates virulence through S-adenosylmethionine (SAM) salvage pathways	Inhibition of autoinducer molecules
6	[29]	*Pseudomonas aeruginos*a		(2-nitrophenyl) methanol derivatives, PqsD inhibitor, inhibits signal molecule biosynthesis	Signaling molecule production inhibition
7	[30]	*Streptococcus pneumonia*		Sinefungininhibits AI-2 synthesis through downregulating luxS, pfs, and speE expression	Inhibition of biofilm growth *in-vitro*
8	[31]	Gram-negative bacteria		FabI derivatives, an inhibitor of enoyl-ACP reductase, promotes acyl chain length of N-acyl homoserine lactones	Signaling molecule production inhibition
9	[32]	*Bacillus* sp. 240B1	Degradation of Signal Molecule	The aiiA gene degrades AHL encoding enzyme	Degrades AHL signaling molecules
10	[33]	*E. coli*, *Haber's bacillus*,*Salmonell a typhimurium*		LsrK initiates DPD as a precursor molecule for AI-2 phosphorylation	Prevention of QS response
11	[34]	*Pseudomonas aeruginosa*		Lactonase SsoPox degrades acyl-homoserine lactones	Inhibition of proteases and pyocyanin secretion and biofilmformation
12	[35]	*Pseudomonas aeruginosa*		Lactonase Aii810 degrades acyl-homoserine lactones and N-(3-oxododecanoyl)-L-homoserine lactone	Inactivation of Virulence Factors and Biofilm Formation
13	[36]	*E. coli*		Exogenous imidazole acts as ananalog of AI-2	Inhibits the function of AI-2
14	[37]	*Pseudomonas aeruginosa*		Overexpression oflactonase enzyme AHL-1 degrades acyl-homoserine lactones	Inhibition of swarming motility and biofilm formation
15	[38]	*P. aeruginosa PAO1*		Lactonase AiiK degrades acyl-homoserine lactones	Inhibition of biofilm formation and inactivation of pyocyanin production
16	[39]	*Bosea*(F3-2),*P. aeruginosa, Pectobacteriumcar otovorum*		AHL lactonase (AidB) hydrolyzes ester bonds of homoserine lactone (HSL) ring	Degradation of AHL signal and production of QS-dependent virulence factors
17	[40]	*Botulinum*, fungal and Gram-positive		Recombinant strain named *Bb*MomL, produced by connecting MomL with	Degradation of AHL signal

		bacterial		pNCMO2, degrades signal molecule C6-HSL and AHL	
18	[41]	*Pseudomonas aeruginosa*		Crude extracts from *Lactobacillus crustorum*, ZHG 2-1degrade AHL	Degradation of AHL signal
19	[42]	*Yersinia enterocolitica*		Flavonoids from *Citrus sinensis* reduce concentration of quorum-sensing signals and inhibits biofilm formation	Inhibits quorum-sensing signals
20	[43]	Cell culture and *Xenopus* embryos	Inhibition of Signal Molecule Conduction/Binding to Receptors	Five different haloquinoneanalogs blocks Wntsignaling downstream of beta-Catenin	Inhibits abnormally activated Wnt/β-catenin signalling
21	[44]	Pathogen		2*H*-pyran-3(6H)-one derivative inhibits Signaling Pathways through Catalytic Enantio-selective Synthesis	Inhibition of Wnt and Hedgehog Signaling Pathways
22	[45]	*P. aeruginosa* PAO1		N-decanoyl-L-homoserinebenzyl ester activates quorum sensing control repressor	Inactivates protease and elastase activity, swarming motility
23	[46]	*Actinomycetes*		AI-2 receptor is bound with D-galactose-binding protein instead of ribose binding protein (RbsB)	Inhibits AI-2 activity and biofilm formation
24	[47]	*Edwardsiellatarda*		Peptide 5906 binds with LuxS thereby preventing formation of functionally identical Lux Sdimmers	Inhibits LuxS activity
25	[48]	*Pseudomonas aeruginosa*		Flavonoids act as allosteric inhibition for LasR and RhlR (AI-binding receptors)	Alternation of transcription of QS-controlled target promoters
26	[49]	*Aeromonas caviae*Sch3		Alkylquinoxaline-2(1H)-one inhibits signalling pathways	Inhibits signalling pathways
27	[50]	*Pseudomonas aeruginosa*		N-(3-oxododecanoyl) homoserine lactone QS binding site blocked by Las R interaction of N-terminal ligand binding domain of LasR	Coupled with ciprofloxacin, it inhibits formation of biofilms and increase antibiotic sensitivity
28	[51]	*Pseudomonas aeruginosa*		Chinese herb extract inhibits binding of MvfR to the corresponding pqsA promoter by acting as a competitor	Suppressesquinolone signaling (PQS) system completely, *rhlR/rhlI*QS system moderately and *lasR/lasI*QS system slightly
29	[52]	*Vibrio parahaemolyticus*		Degradation of acyl-homoserine lactones by AHL-lactonase(AiiA)	Inhibition of biofilm formation
30	[53]	*Chromobacterium violaceum* CECT 5999, *Pseudomonasaeruginosa* ATCC10145	Inhibition via anti-QS agents	Acylase from *Aspergillus melleus* degrades C6-LHL	Inhibition of violacein production and biofilmformation
31	[54]	*Pseudomonas aeruginosa* ATCC10145 and PAO1		Acylase from *Aspergillus melleus* degrades C4-LHL, C6-LHL, and3-oxo-C12-LHL	Reduction in biofilm formation and pyocyaninsecretion
32	[55]	*Aeromonas hydrophila*		AHL lactonase AIO6 degrades acyl-homoserine lactones	Lowers microvilli length
33	[56]	*Pseudomonas aeruginosa* PAO1		Acylase (EC.3.5.1.14) d Degradation of AHL inducers	Reduction in biofilm formation
34	[57]	*Vibrionaceae strains*		Removal of AHLs genes leads to Acyl-homoserine lactones inactivation	Reduction in virulence of mutantstrains

Many recent works focus on the indirect regulation of MDR strains by modifying the quorum-sensing signal molecules or synthesizing some structural analogues to those of concerned quorum-sensing signal molecules. Quorum sensing is a common practice for bacterial species to communicate with

each other through specific gene regulation. This is achieved by the production of certain signal molecules called autoinducers. The microbial population directly impacts the amount of these signal molecule production [58].

The alternation or change in signal molecules could be due to their degradation [36, 39, 41] or the addition of competitive inhibitor molecules that would block the signal molecule binding to receptors [47, 49-51]. Inhibition of quorum sensing signalling through inhibiting the AHL signal generation can be achieved in three ways *viz*. affecting the synthesis of the substrates for AHL synthase *i.e*., fattyacyl-acyl carrier protein (acyl-ACPs) by inhibitors; inhibiting N-acyl homoserine lactone (AHL) synthesis directly; and by inhibiting the HLAs transport [59]. In a study, Picomolar inhibitor, MT-DADMe-ImmA has been synthesized through 5′-methylthioadenosine phosphorylase (MTAP) that blocks QS in *Vibrio cholerae* without affecting growth rate and inhibits QS signal AI-2 [25].

Similarly, regulation of quorum sensing by affecting the signal reception is also crucial and follows various ways. These are direct AHL degradation to limit signal turnover, segregation of the AHL signalling pathway, and competition on AHL receptors with suitable AHL-mimetic compounds. The degradation mechanism of signal molecules uses quorum-quenching enzymes produced by microbes leading to less concentration of signal molecules below the threshold. This will directly affect the microbial gene expression and generation of any virulent factors. A similar mechanism of QS regulation was followed where the aiiA gene degrades AHL encoding enzyme, thereby degrading AHL signalling molecules in *Bacillus* sp. 240B1 [32]. The quorum-sensing system using AHL signal molecules degradation method for many pathogenic bacteria can be a vital virulence regulator. It showed greater efficacy as no regulation was imposed on the pathogen itself; however, their signal molecules are targeted. Moreover, Signal molecule attenuation or degradation can be achieved using QS to prevent bacterial resistance. Many microbes can metabolize AI-2, leading to the inhibition of QS function. AI-2 can be phosphorylated outside the cell by the addition of ATP and LsrK, which are then unable to pass through the cell membrane as QS signals [60]. This mechanism was widely accepted and backed up by several other studies [39-41].

Moreover, quorum-inducing signal inhibitors also help in the reduction of pathogenicity. The addition of competitors achieves this. Many living organisms secrete several compounds that are quorum-sensing signal analogues and can competitively bind with microbial quorum-sensing signal receptors, thereby interfering with their regulation system. This leads to a decrease in the pathogenicity [22]. Several studies showed similar results [49-51]. The study showed that the five different halo quinoneanalogues in Cell culture and *Xenopus* embryos block the Wntsignalling downstream of beta-Catenin, thereby inhibiting the activated Wnt/β-catenin signalling [43]. Similarly, the anti-QS molecules can also help in diminishing the QS signalling, thereby preventing bacteria's pathogenicity, its resistant activity, and biofilm formation. It will directly block the development of drug-resistant to pathogens [53-57, 61].

CONCLUSION: Bacterial quorum sensing (QS) signalling, consisting of acyl-homoserine lactones (AHLs), autoinducing peptides (AIPs), and autoinducer-2 (AI-2), plays a pivotal role in balancing its pathogenesis. The alternatives to antibiotics are in high demand nowadays due to the increase in the resistance factor of pathogens. The most suitable one currently is an alteration in the signal molecule production by several strategies, including their inhibition or degradation or blocking of receptor molecules or utilization of anti-QS agents. These methods help in the reduction of bacterial virulence, thereby inactivating them.

However, elaborate studies on this aspect provide an alternate method to suppress or degrade the virulence activity of microbes due to their increased multi-resistant capacity. Hence, multi-regulatory mechanisms have to be utilized in view of the current QS-related, related research should be further improved by means of molecular biology. The complex microbial drug resistance system should be well studied, and efficient QSI screening methods should be adopted. Multiple QS regulation compounds in bio-active compounds, suppressing elements, or targeting genes should be considered more.

The study related to the formation of microbial resistance mechanisms and their regulation through different strategies is the current approach that deals with the regulation of the quorum-sensing system. It not only has a role in microbial pathogenesis but has an active involvement in bacterial biofilm formation and its regulation. Hence breakthrough in research related to quorum sensing and its regulatory systems on microbial-resistant pathogenicity has several alternatives and are the main focused area for future research.

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