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Review

The Role of Quorum Quenching in Medical Application

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ABSTRACT

The attempts are continuing in the various fields of life sciences to resolve a big problem, which is the ability of bacteria to cause pathogenicity for humans, animals, and plants, whether by chemical or biological methods and in ways that are hoped to be safe. Among these attempts, the control of the Quorum Sensing (QS) mechanism that occurs naturally in bacteria under certain conditions helps to increase the virulence of bacteria, starting from its ability to adhere and form a biofilm. Then, the tissues are invaded with various enzymes according to the tissue type, increasing antibiotic resistance. Therefore, the idea came to solve these problems through a mechanism opposite to the Quorum Quenching (QQ), which lies in the investigation of substances that can disrupt the QS pathway, whether at the molecular level or the physiological level, as well as benefiting from different organisms (Prokaryotes or Eukaryotes) that live in the same environment and produce substances that inhibit bacterial signaling molecules. Lastly, the discovery of varying novel QQ agents from extreme environmental bacteria will be most interesting in the future.

Keywords: Quorum sensing, quorum quenching, acyl homoserine lactones, medical application.

INTRODUCTION

The population density and bacterial behavior in different environments are regulated by a specific mechanism known as Quorum Sensing (QS). Small molecules responsible for QS are called signaling molecules or Autoinducers (AIs), sensed by intracellular or membrane-bound receptors in the producer cell or other bacterial cells in the population [1, 2].

There are different types of AIs according to their chemical structure and mechanism of action. The main types of AIs are (i) Acyl Homoserine Lactones (AHLs) that are used by gram harmful bacteria, (ii) Auto-Inducing Peptides (AIPs) in gram-positive bacteria [3]. Other references add a third type of AI: furanosyl diester borate (AI-2) [4]. Meanwhile, others divide AI-1 into two types: AHLs that carry out intraspecies communications and AI-2 that involve furanosyl borate interspecies communications. [5]. Furthermore, studies can provide additional AI types, such as fatty acids (FA), quinolone in *Pseudomonas* spp., and butrylactone in *Streptomyces* spp. [1].

Various AI types have the same function as QS molecules when their concentration increases to a certain level. At this concentration level, AIs bind with their receptors (Figure 1). This binding stimulates the regulation of specific genes [6, 3].

AHL molecules may perform other functions as antibacterial agents, mainly when composed of long carbon chains [7], such as N-3-oxo-dodecanoyl-L-homoserine Lactone (OC12-HSL), which are named bacteriocin when they act as antibiotics [8].

Cascades of QS enhance virulence factors such as biofilm production, plasmid transfer, enzymes, and motility. Also, QS gives additional bacterial adaption properties to harsh environmental conditions and activation of bioluminescence in *Vibrio fisheri* bacteria [9, 6].

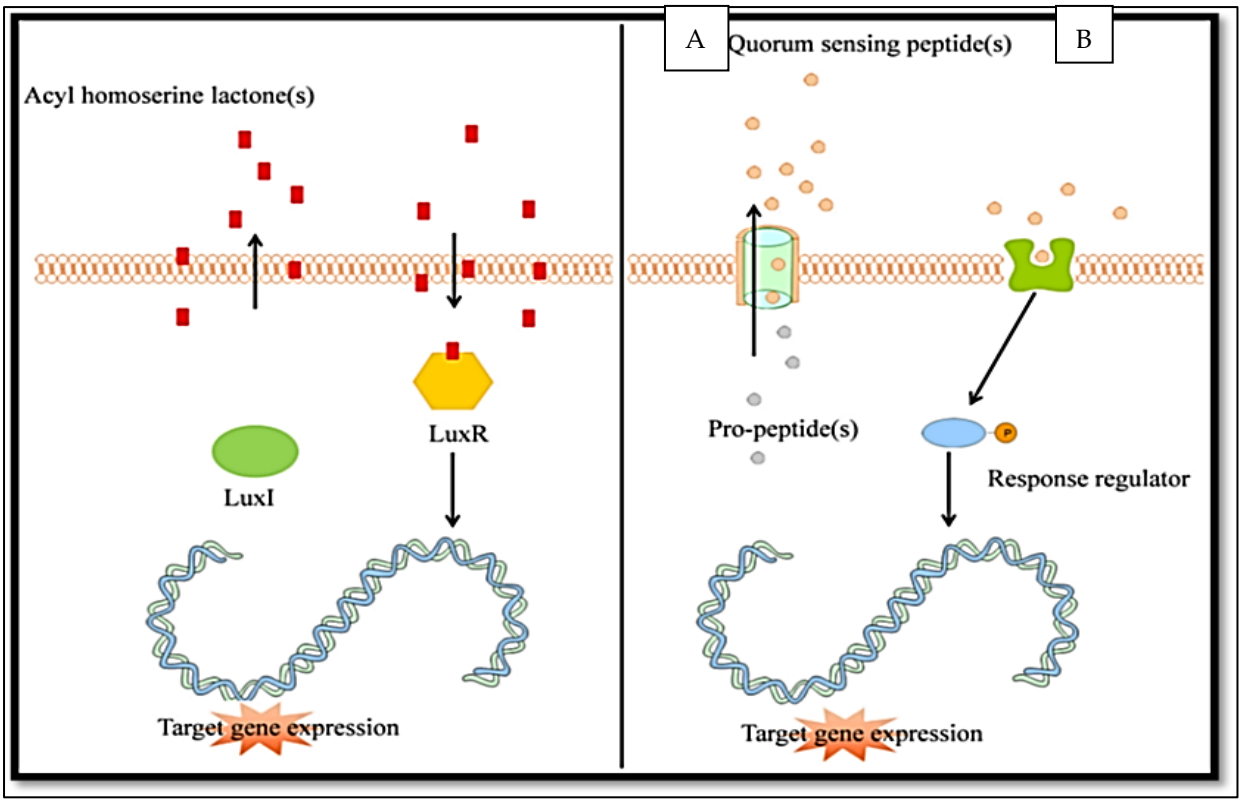

Figure 1: The quorum sensing mechanism. A: in Gram-negative. B: in Gram-positive bacteria [3].

QUORUM QUENCHING (QQ)

The Quorum Quenching (QQ) is a molecular mechanism of processes that interrupt bacterial communication; it is achieved by several modes of action [10- 12]. QQ was first discovered in *Erwinia carotovora,* which produces AHL-degrading enzymes that cause QS blocking [12, 13]. QS Pathway consists of multiple steps. Each step can be interfered with by specific QQ molecules, also called QS inhibitors (QSIs). Biological molecules and other physical factors such as pH and temperature can act as QSIs. [6].

The competitive inhibitors for AI molecules can be biosynthesized from microorganisms such as bacteria or eukaryotic organisms like algae, marine animals, plants, and fungi. These inhibitors block AIs-receptors binding, leading to QS disrupting [14]. Extracellular QQ enzymes can degrade or modify AIs. These enzymes produce bacteria with competitive advantages to get nutrients in their environments [15, 16].

There is no pathogenic commensal flora present in healthy skin. When the skin is exposed to wounds, lesions, and burns, this flora colonizes damaged skin, multiplying and forming biofilm. Signaling molecules AIs produce a biofilm that enables bacteria to become more virulent and resistant to antibiotics, phage therapy, and antibody goals. However, the QQ molecules that are used against biofilm bacteria remain not harmful and without defenses (Figure 2). Therefore, QQ helps cure unhealthy skin and helps it stay in a noninfectious state [17].

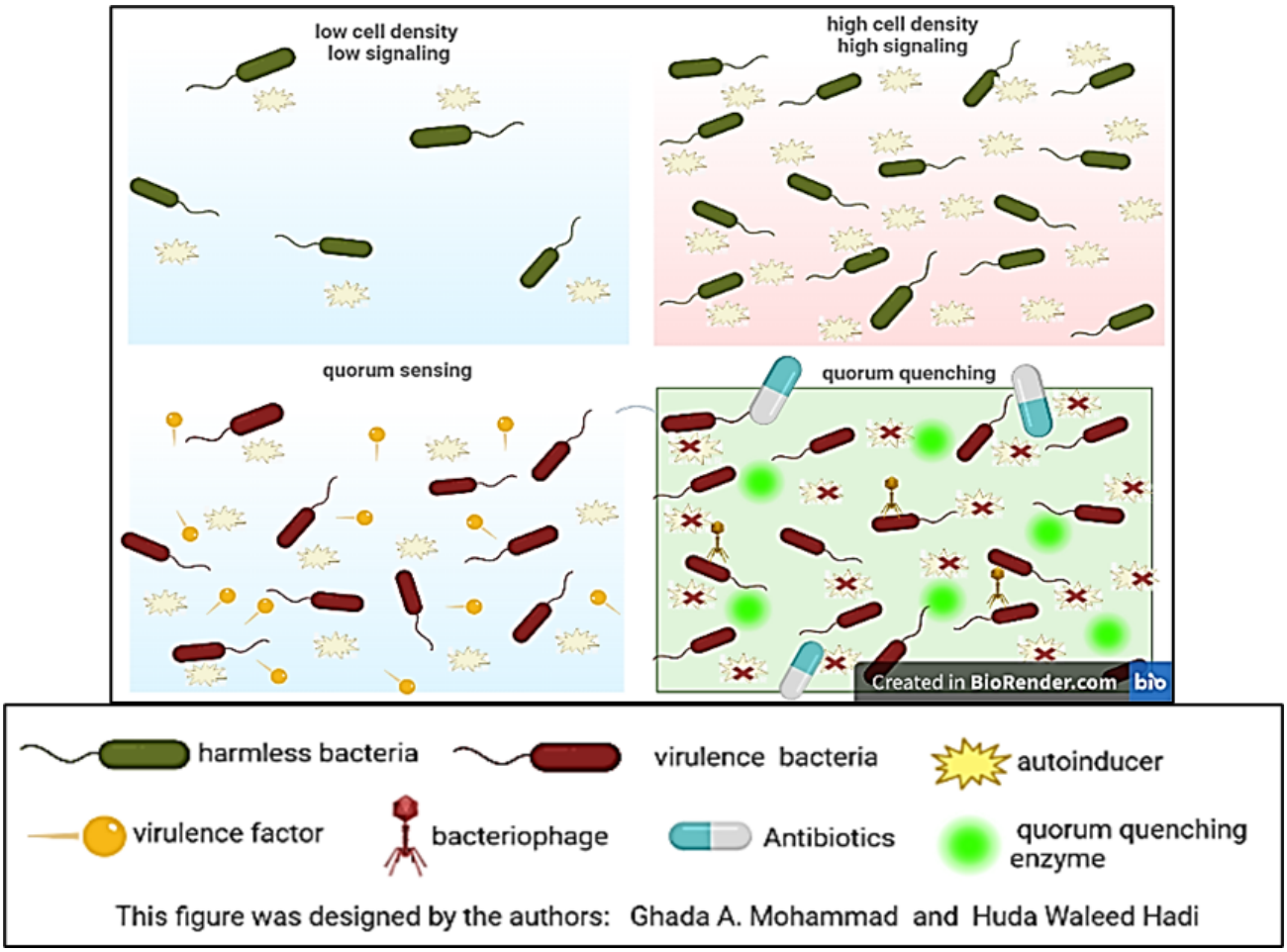

Figure 2: Quorum sensing vs. quorum quenching in this review.

FIRST: NATURAL COMPOUNDS

Natural compounds have important antibacterial features and anti-virulence characteristics. QQ molecules from natural compounds, either eukaryotic or prokaryotic sources, are efficient and safe. They are readily biodegradable and can interrupt bacterial infection in a very active manner [18, 19].

A- Bacterial QSIs

Bacterial QQ molecules are isolated from different bacterial taxa such as Firmicutes, Actinobacteria, Proteobacteria, Bacteroides, and Cyanobacteria. These bacterial QQs are very active against *Pseudomonas aeroginosa* biofilm producers and also have an essential role in biofilm removal in the wastewater treatment plant. The bacteria produce three types of enzymes: AHL lactonase, AHL acylase, and AHL oxide reductase [13, 11]. Other references add a fourth class to these enzymes to become four classes by separating oxidase enzymes such as cytochrome from reductase enzymes [20, 1].

AHL-Lactonase Enzymes

This type of enzyme belongs to the Metallo-β-Lactamase (MBL) family [11]. Some references further divided the lactonase enzymes in addition to the previous class according to their protein folding and active motif, such as the Phosphodiesterase- Lactonase (PLLs), the α/β hydrolase fold lactonase, and the paraoxonase. Classes of lactonase have been observed evolutionary convergence with low specificity to the substrate level except PLLs that show high specificity to the long chains AHL [16, 21]. Lactonase enzymes can degrade or modify the lactone ring (Figure 3) in different molecules of AHL, therefore blocking swarming motility in *P. aeroginosa* by lactonase produced by *Pectobacterium carotovora*[22]. Hence, they are efficient in interfering with QS. AHL-lactonase enzymes have been isolated from various prokaryotic, archaea, and eukaryotic

organisms. They have been assessed in their controlling of different diseases. Therefore, increasing their effectiveness activity by engineering studies leads to the rise of their catalytic activity and stability [23].
Lactonase enzymes do not interfere with QS only; they can interfere with other biological processes, such as the bacterium *Agrobacterium tumefacien*t, which is controlled by Ti plasmid [24, 1].

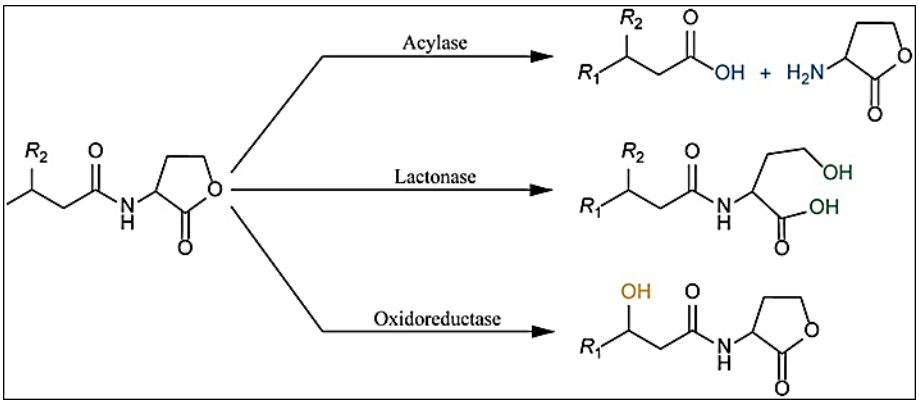

Figure 3: Prokaryotic Enzymes Action on AHL molecoule [25].

AHL-Acylase Enzymes

Acylase enzymes separate acyl chains from lactone rings (Figure 3). Amidase enzymes (or acylase) are considered from this type of enzyme. *P. aeroginosa* can degrade the AHL molecules by its amidase enzymes [1].
It has been proved that treatment of wastewater biofilms by AHLs degrading enzymes (Aculeacin A Acylase (AuAAC) which is obtained from Actinoplanes utahensis) can prevent the four systems of QS in *P. aeroginosa* [13].
AHL-acylase enzymes belong to the family of N-terminal nucleophilic hydrolases (Ntn- hydrolases). PvdQ is an example of these enzymes that can split an acyl chain with more than 10 carbon atoms [16].

AHL-Oxidoreductase Enzymes

These enzymes can modify the AHL molecules without degrading them (Figure 3). They can reduce or oxidize AHL molecules [26]. Oxidoreductase enzymes spread in the bacteria that used AHL molecules as nitrogen or carbon sources [11]. also include oxidoreductase and esterase enzymes [26].

B- Eukaryotic QSI

Varieties of QQ eukaryotic molecules have been isolated from different taxa of the eukaryotic cells. These molecules are very active as QQ; therefore, they have essential roles in medical fields[20,27]. Eukaryotic enzymes have been extracted and purified from different animals, which can disrupt QS signals, such as the acylase 1 enzyme of porcine kidney [28]. paraxonases 1, 2, 3, and QQ enzymes are found in epithelial cells and mammalian sera [29].
However, the plant extracts represent valuable and safe compounds for disrupting the bacterial QS (Table 1). Because of the ability of these compounds to disrupt bacterial infection without causing antibacterial resistance, QQ phytocompounds are very important in fighting bacterial virulence and antibiotic resistance, especially in *P. aeruginosa* [19].
Isolated substances from fungi also have a role in the QS blocking, such as ethyl acetate extracts from *Plectosphaerella cucumerina* fungus against *P. aeroginosa* PAO1 strain; the treatments by the fungal compounds lead to a high potential in blocking the biofilm formation without killing the producing bacteria[30].
The marine red algae *Halemenia durvilleican* produces metabolites that disrupt the AHL in gram-negative bacteria such as *Klebsiella pneumonia* and *P. aeroginosa* [31]. Complex reactions can occur in the relationships between algae and QS-associated bacteria, which may affect their ecology system [32].

Quorum Sensing Inhibitor Compounds	Quorum Sensing Efficacy
Curcumin	Motility phenotypes and production of biofilm
Flavonoids (naturally-produced plant Metabolites)	LasR and RhlR receptors
Ajoene, a Sulfur-Rich Molecule from Garlic	Pathogenic factors production
Salicylic acid	Secretion of protease, elastase, pyocyanin and production of biofilm and the expressions of lasI, lasR, rhlI, rhlR genes
Clove oil	Protease, chitinase and pyocyanin secretion, swimming motility and production of biofilm
Caffeine	Motility phenotypes
Allium sativum (Garlic) extract	Production of biofilm, elastase secretion

Table 1: The Herbal Extracts as Quorum Sensing Inhibitors [11]

SECOND: SYNTHETIC QSI

The use of nanoparticles (NPs) and engineering nanoparticles as antimicrobial agents gained importance in previous years because of the increased bacterial resistance to ward antimicrobial agents. NPs have little or no toxicity and have pharmaceutical properties as antibiotics [33, 34, 35]. Other studies suggested that NPs can be used as anti-QS signals. Because of its ability to penetrate the biofilm, genes cascade and stop cell-to-cell signaling, which leads to the cessation of biofilm formation [33, 36].

Cationic polysaccharides chitosan NPs have many clinical properties, but the important one is anti-QS signals. It has a positive charge that reacts with the negative charge of the lipopolysaccharides in *the P. aeroginosa* cell wall. This reaction causes membrane permeability changes, leading to bacterial killing; furthermore, the NPs can affect the virulence factors such as pyocyanin and protease gene expression of biofilm formation [37].

The zinc oxide NPs can combat *P. aeroginosa* signals such as rhamnolipid, pyocyanin, pyoverdin, hemolysin, elastase, and protease in addition to the inhibition of QS genes, which leads to a decrease in the pathogenicity and virulence of *P. aeroginosa* in vivo [38].

Quorum Quenchers Application

The QQ has an essential role in the medical field, health care, aquaculture, agriculture purposes, phytochemicals, antibiotics, and water engineering [39].

Quorum Quenching in Medical Application

The QQ controls various virulence factors such as sporulation, biofilm formation, enzyme production, motility, pigment production, flagella, and pili[40]. Also, biofilm formation is the main problem that makes most diseases, such as oral cavities and cystic fibrosis, hardly curing[41].

There are several mechanisms in the medical application of QQ, such as:

1- Using synthetic analogs of AHL molecules, which disrupt the binding of AHLs with their receptors, can also alter the chemical function of the acyl chain tail or the head of AHL molecules [42].
2- Using engineering QQ enzymes such as lactonase and acylase isolated from various organisms may become more efficient in the degradation of AHL molecules [23].
3- Down-regulation of the bacterial virulence genes by Qs inhibitors using trans-cinnamaldehyde and salicylic acid in QS inhibition of *P. aeroginosa* PAO1 strain [43].
4- Blocking the signaling cascades [44].
5- Inhibition of the signal molecules' biosynthesis [45].

In the field of Medical Devices

Most Hospital Acquired Infections (HAIs) are associated with using various contaminated medical devices [46]. The emergence of QQ molecules in synthesizing various medical devices is a very useful method to avoid

HAIs (Table 2). The recent generation of catheters, trauma, dressing, aerosols, contact lenses, and implantable devices are involved in QQ molecules [17]. For example, device surfaces coated with pro and anti-QS peptides show high antibacterial potential against *Staphylococcus aureus* strains [47].
Medical devices containing QQ require further testing with more pathogenic and virulent bacterial strains. Therefore, researchers seek to use highly resistant QQ enzymes or compounds isolated from microorganisms of extreme environments, such as *Solfolobus solfataricus* [17].

QQ strategy	QQ agent	Application
QSI	5-fluorouracil	Catheters
	Thiazolidinedione-8	Urinary catheters
	Furanone and DHP	derivatives Implanted medical devices
Peptides	Macrocyclic peptides	Nanofiber coatings
	RNAIII-inhibiting peptide	Dacron graft
QQ Enzymes	Acylase from A malleus.	Catheters and other coated devices
	Lactonase from *Bacillus* sp. ZA12	Topical treatments
	AI-2 processing kinase LsrK	Capsules
Natural compounds	Polyphenols of honey	Nanovectors

Table 2: Quorum quenching-based medical devices [17].

QQ-Based Antibacterial Treatments in Medicine

Conventional antibiotics cannot penetrate the extracellular matrix of bacterial biofilm, which leads to the loss of 80% of their efficiency. The infections caused by biofilm production in oral cavities and cystic fibrosis occur directly via this biofilm, and most infections associated with HAIs result from biofilm contamination of medical devices[48 41].

Antibody-based QQ efforts

The blocking of bacterial cell communication via the use of monoclonal antibodies (mAbs) is a beautiful strategy to prevent infections. These mAbs can also detect homoserine lactones (HSLs), which control QS system-dependent LuxI/LuxR in *P. aeroginosa.* The groups of mice treated with the QQ mAbs are found to be protected and cured from pneumonia caused by *P. aeroginosa* compared with control groups [49].
The mAbs-based QQ have acquired importance in recent years because of their high specificity and little toxicity; they also can degrade the signaling molecules by inhibiting the pyocyanin production in *P. aeroginosa*[50].

Antibiotics as QSI

Antibiotics cannot inhibit the growth, metabolic activities, or cell wall synthesis of bacteria only. Still, they also interfere with the QS pathways as macrolides and β -lactam antibiotics, inhibiting the several appearances of QS[51].
Azithromycin, imipenem, cefepime, tazobactam, and piperacillin were examined as antivirulence factors of wild and mutant *P. aeroginosa* strains. Virulence factors include pyocyanin, biofilm, hemolysin, protease, and DNAse, all of which depend on QS signals. Antibiotics in their sub-inhibitory concentration (SIC) can interfere with QS better than the highest concentrations and do not cause the appearance of antibacterial resistance and side effects[52].

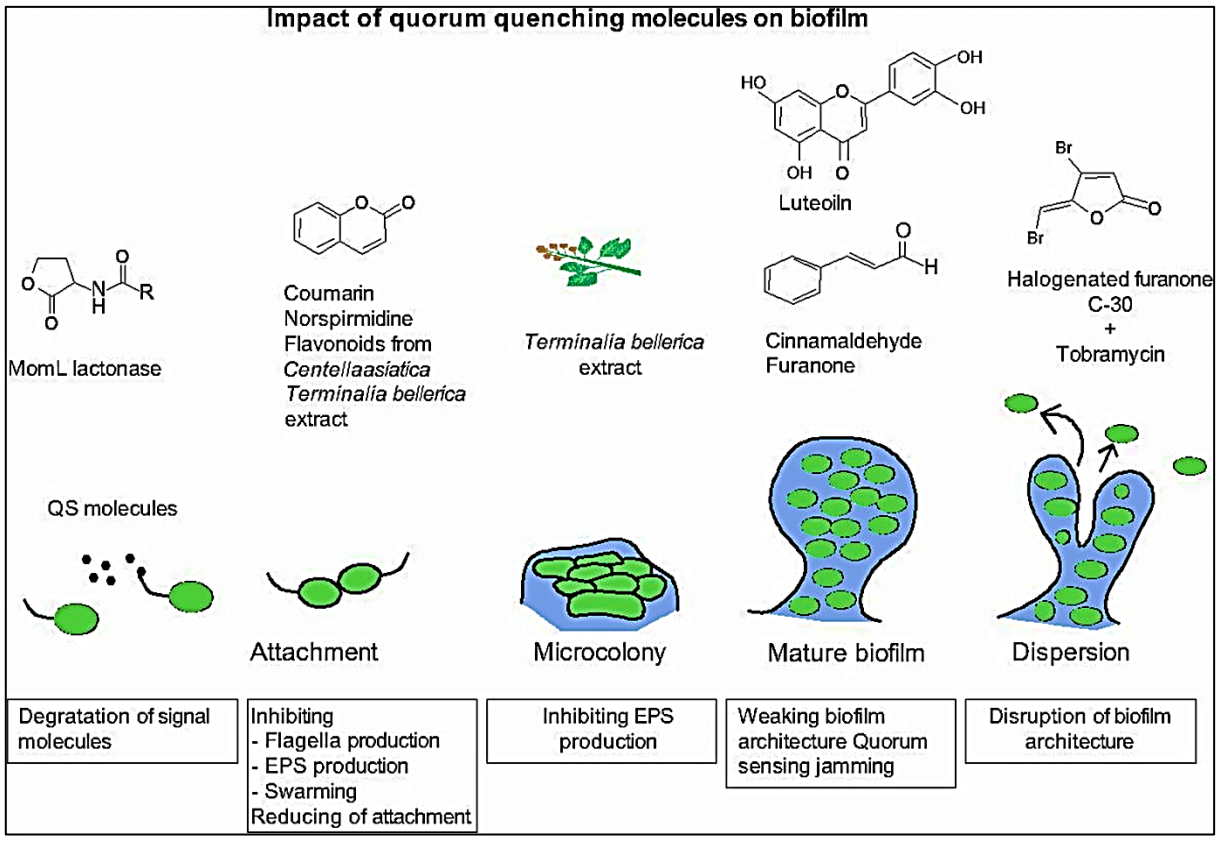

Figure 4: The impact of quorum quenching molecules on biofilm formation [6].

Similar results with *P. aeroginosa* and *Acinetobacter baumannii*, which are considered from MDR bacteria, were obtained by the study of Saleem and co-workers, who mentioned that the Erythromycin, chloroquine, and propranolol antibiotics were able to inhibit (in SIC) virulence based on QS such as biofilm, enzymes, resistance to oxidative stress, swarming and twitching [53].

CONCLUSIONS

As bacterial response mechanisms are regulated by what is known as Quorum Sensing QS, other mechanisms meet it and work to stop it, and they are called Quorum Quenching QQ. Both QS and QQ mechanisms are diverse and vary with a wide range of chemical compositions. So, scientists compete to reach the most efficient means of QQ by various means to eliminate the bacterial pathogenicity and virulence factors, especially in resistant pathogenic bacteria. Nowadays, the QQ methods represent a global goal to eliminate antibiotic resistance mechanisms that have recently spread comprehensively. Therefore, this article highlights the most important and latest applications based on QQ, especially medical equipment and devices in direct contact with the patient's life, to eliminate hospital nosocomial infections and the widespread bacterial resistance to the latest choice of antibiotics.

Conflicts of Interest: "The authors declare no conflict of interest." "The funders had no role in the study's design; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results."

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