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Review article

Quorum sensing interference by phenolic compounds – A matter of bacterial misunderstanding

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ABSTRACT

Over the past decade, numerous publications have emerged in the literature focusing on the inhibition of quorum sensing (QS) by plant extracts and phenolic compounds. However, there is still a scarcity of studies that delve into the specific mechanisms by which these compounds inhibit QS. Thus, our question is whether phenolic compounds can inhibit QS in a specific or indirect manner and to elucidate the underlying mechanisms involved. This study is focused on the most studied QS system, namely, autoinducer type 1 (AI-1), represented by *N*-acyl-homoserine lactone (AHL) signals and the AHL-mediated QS responses. Here, we analyzed the recent literature in order to understand how phenolic compounds act at the cellular level, at sub-inhibitory concentrations, and evaluated by which QS inhibition mechanisms they may act. The biotechnological application of QS inhibitors holds promising prospects for the pharmaceutical and food industries, serving as adjunct therapies and in the prevention of biofilms on various surfaces.

1. Introduction

A simple search in the main databases confirms a sharp increase in the number of publications over the last ten years involving quorum sensing (QS) inhibition by phenolic compounds. For example, publications on Scopus database that feature the terms "quorum sensing" AND "phenolic compound" (within all fields) increased from 72 (in 2012) to 616 (in 2022). Publications involving "quorum sensing inhibition" in the ScienceDirect platform also increased considerably, showing the growing interest in the topic.

The antimicrobial activity of plant-derived compounds is also well discussed in the literature. In fact, the main source of natural quorum sensing inhibitors (QSIs) are plants, including vegetables, fruits, roots, rhizomes, flowers, leaves, and seeds [1]. The role of plant-microbial interaction is well studied between plants and the pathogen *Agrobacterium tumefaciens* as well as between plants and their nitrogen-fixing symbionts of the genus *Rhizobium* and its allies, often involving phenolic compounds [2,3]. The compounds produced by the secondary metabolism of plants are grouped into several classes, with phenolic compounds being the most studied group due their abundance and bioactive properties, such as antimicrobial, antioxidant and anti-inflammatory activities [4,5].

However, the number of publications focused specifically on elucidating the mechanisms behind QS inhibition is still limited compared to the body of literature that evaluates the inhibition of QS regulated phenotypes by plant extracts or isolated natural compounds. The question that remains is whether phenolic compounds, or any other natural compound, specifically inhibit QS and if so, by which mechanism. Given the pleiotropic effects of phenolic compounds on cellular mechanisms, the question provokes

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thoughtful consideration and may not have a straightforward answer as initially anticipated.

In this review, the recent literature was analyzed in order to understand how phenolic compounds act in the cell at sub-inhibitory concentrations and in which QS inhibition mechanisms they may interfere.

A literature search was conducted in the period of September 2021 to May 2022 using the standard databases Scopus, PubMed, Web of Sciences, SciELO, Google Scholar and ScienceDirect with no data limitations. Key search terms included: "quorum sensing", "quorum quenching", "quorum sensing inhibitors", "phenolic compounds", "AHL", "Acyl homoserine lactones", "Gram negative bacteria", "mechanisms", "modes of action", "plant-derived compounds", "phenolic compounds", "quorum quenching enzymes" usually using the operator AND. The authors examined the article's abstracts and included those that fell within the scope of the present review. Experimental articles that did not present minimal inhibitory concentration (MIC) analysis of phenolic compounds, but still presented results on QS inhibition were excluded.

In the present work, we first present a brief overview of the general QS mechanisms as well as a detailed view on QS mediated by AHLs; we then go on to summarize advances in ways to achieve QS inhibition and the possible advantages of this strategy and, finally we present a critical view of the literature in order to answer the main question of this search - do phenolic compounds specifically inhibit QS or is the inhibition a secondary consequence of a more general inhibition?

2. General mechanisms and key components of QS systems

Even though bacteria are classified as single celled organisms, that does not mean they live independently. They possess sophisticated communication systems that enable them to send and receive chemical messages to and from other bacteria [6,7]. This mechanism is a type of communication known as quorum sensing (QS), which is based on the production, secretion, and response to extracellular signaling molecules called autoinducers, whose concentration correlate with the populations' cell density [8–10]. This process is stimulated through the recognition of a threshold stimulatory concentration of signaling molecules, which allows communication between cells, leading to the expression of specific target genes [11,12]. Therefore, QS enables bacteria to monitor the environment and act as a group, which facilitates population-dependent adaptive behavior, such as bioluminescence, biofilm formation, production of toxins, sporulation, conjugative DNA transfer, among others [1,13,14].

The first ground-breaking proof of QS as a model of cell-to-cell communication in bacteria began in the 1970s, with the observation that bioluminescence in a marine gammaproteobacterium *Vibrio fisheri*, now *Aliivibrio fisheri*, is controlled by the secretion and detection of signaling molecules after a certain population threshold is reached [15]. However, the term "quorum sensing" was used for the first time two decades later by Fuqua, Winans and Greenberg, three researchers who have made extensive contributions to the field [9].

The advance in the field showed that different QS circuits exist depending on the organism, mediated by an extensive lexicon of signaling molecules [16]. At low population densities, production and secretion of QS signaling molecules occur at a basal level. As cell

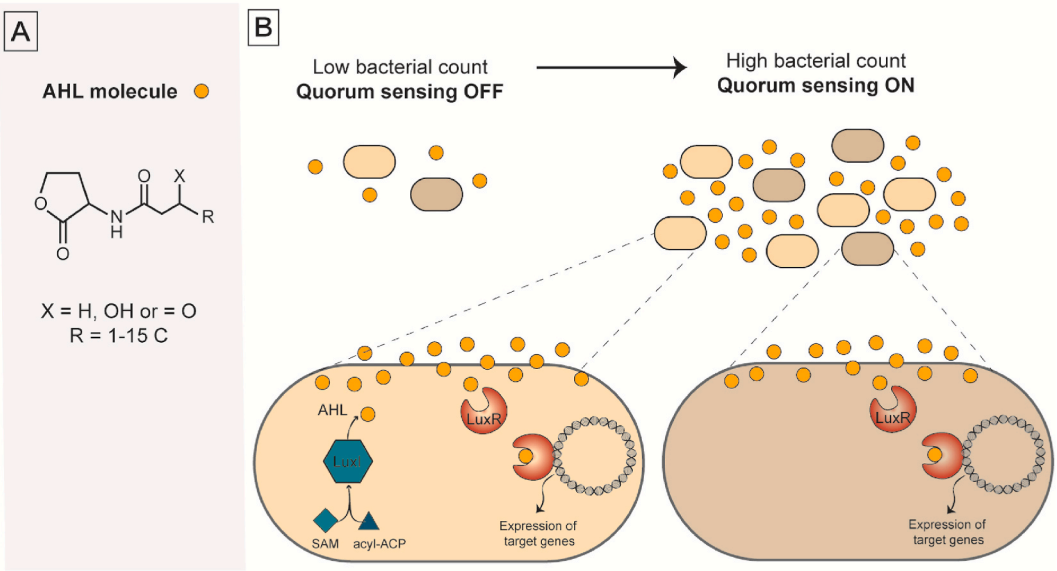

Fig. 1. A typical Gram-negative QS system. **A**: general structure of an acyl homoserine lactone molecule (AHL). R can vary from 1 to 15 carbons. **B**: Activation of QS occurs at high concentration of signaling molecules, usually at high cell densities. In light beige cells (on the left), a complete QS system: AHLs, synthesized by a LuxI-type enzyme, passively diffuse through the bacterial cell membrane and when a threshold level is reached, they activate the intracellular LuxR-type transcription factor which subsequently activate target gene expression in a coordinated way. Some bacteria (dark gray, on the right) may possess a so-called LuxR solo protein, lacking a LuxI-type protein and the ability to synthesize their own AHL molecule, but still being able to respond to AHLs produced by other bacteria.

density and concentration of signaling molecules increase, so does the synthesis of signal producing proteins (enzymes), establishing a positive feedback loop which is proposed to promote synchronous gene expression in the population. This process is often referred to as autoinduction [12,14,17].

Autoinducers (AI) are chemically diverse molecules and conventionally divided into three major groups: *N*-acyl homoserine lactones (AHL, or AI-1), used by proteobacteria, are the most common class of autoinducers; oligopeptides or auto-inducing peptides (AIPs) used by Gram-positive bacteria [18]; and AI-2, a group of molecules derived from 4,5-Dihydroxy-2,3-pentanedione (DPD), found in both Gram-positive and negative bacteria, which is thought to be a type of interspecies communication mechanism [19,20]. New molecules have been discovered indicating alternative types of QS signaling mechanisms, such as the *Pseudomonas* quinolone signal (PQS, 2-heptyl-3-hydroxy-4(1H)-quinolone)) and its precursor HHQ (2-heptyl-4(1H)-hydroxyquinolone) [21]; the autoinducer-3 (AI-3), recently characterized in *Escherichia coli* [22]; indoles [14] and many others.

Although all known QS mechanisms differ in the regulatory components, they are dependent on common features, including production of small signaling molecules (AI) and diffusion or transport through the bacterial membrane; detection of AIs by specific receptors, either in the inner membrane or in the cytoplasm; and activation of target genes that underpin various biological processes including cooperative behaviors [17].

Several clinically important bacteria regulate virulence gene expression through QS systems, which are not essential for bacterial survival outside the host [1] but play important roles in pathogenesis and human infections [23]. Some examples are the expression of virulence factors, surfactants, toxins, antibiotic biosynthesis, surface motility, sporulation, bioluminescence, and many others [17, 23–25]. The expression of these phenotypes in proteobacteria is discussed below.

2.1. *N-acyl homoserine lactone (AHL)-mediated QS system*

The *N*-acyl-homoserine lactone (AHL) mediated QS signaling system is widely recognized as the most extensively studied and well-known mechanism utilized by Gram-negative bacteria. These signaling molecules are composed of fatty acyl chains ranging from 4 to 18 carbons, linked to a lactone ring through an amide bond, and may have a 3-oxo or 3-hydroxy substitution at carbon 3 of the chain (Fig. 1-A). LuxI-type synthases produce AHL by catalyzing the amide bond formation between the substrates *S*-adenosylmethionine (SAM) and the acyl group carried by an acyl carrier protein (ACP) [26]. These molecules are recognized by compatible and selective LuxR-type proteins promoting a certain level of specificity to cell-cell communication in Gram-negative bacteria [7,14,27].

The mechanism of AHL-mediated QS starts with the accumulation of AHL in the environment, depending on bacterial density. Once a threshold concentration is reached, the AHLs are internalized and bind to LuxR-type receptors which are cytoplasmic transcription factors [17]. LuxR proteins contain two functional domains: an amino-terminal ligand-binding domain (LBD) and a carboxy-terminal DNA-binding domain (DBD). The LuxR-AHL complexes are stable, dimerize and bind to DNA regulating expression of specific target genes, according to the species. Additionally, autoinducer binding is required for protein folding of some LuxR-type regulators. By contrast, some types of unbound LuxR proteins are rapidly degraded (Fig. 1) [11,28,29].

Quorum sensing plays a key role in the virulence of *Pseudomonas aeruginosa*, a major opportunistic human pathogen, especially dangerous to cystic fibrosis patients and burn infections [30]. This bacterium has become one of the main model organisms in QS research, since the QS network is well characterized, regulates the expression of multiple virulence factors, besides the importance of this bacterium to the medical community due to antibiotic resistance [31,32]. The QS network of *P. aeruginosa* consists of four interconnected systems, namely *las, rhl, pqs* and *iqs*, organized in a hierarchical manner. Two LuxI/LuxR-type synthase/receptor pairs, LasI/LasR and RhlI/RhlR, are central to the QS network. LasI resides at the top of the hierarchy, synthesizing the AHL called *N*-3-oxo-dodecanoyl-L-homoserine lactone (3-oxo-C12-HSL), which binds to LasR and directs the expression of various genes. Likewise, RhlI produces *N*-butyryl-L-homoserine lactone (C4-HSL) that binds to its RhlR cognate transcription regulator, activating a suit of other genes [10,12,31].

These LuxI/LuxR-type systems, including LasI/LasR and RhlI/RhlR in *P. aeruginosa* mediate inter-cellular communication. However, many bacteria possess LuxR-type AHL receptors that lack a cognate LuxI AHL synthase in their genomes. These unpaired LuxR-family proteins have been called 'orphans' [33] or 'solos' [34], since they act on their own without the need for a cognate signal generator [11,34]. In the absence of LuxI synthases, they can detect different AHL molecules produced by other bacterial species, thus mediating interspecies communication [14]. Curiously, some orphan LuxR proteins can also respond to non-AHL self-produced signals, such as members of the genus *Photorhabdus*: one species uses an orphan LuxR to detect α-pyrones and other species detect dialkylresorcinols and cyclohexanediones, mediating an intraspecies signaling [35]. Finally, some orphan LuxR homologues present in plant-associated bacteria activate the transcription of specific genes in response to small molecules produced by the host plant, comprising an interkingdom signaling mechanism [35,36]. Examples of LuxR solos are QscR of *P. aeruginosa*, ExpR of *Sinorhizobium meliloti*, BisR of *Rhizobium leguminosarum* [34], XccR, OryR and XagR of xanthomonad [36] and SdiA of *Escherichia coli* and *Salmonella*, which can also respond to AHL produced by other bacteria [37] (Fig. 1-B).

Although most members of the LuxR family are AHL-dependent transcriptional activators, several are not. Some members are AHL-inhibited activators, while others are AHL-dependent repressors, and still others are AHL-inhibited repressors [38].

2.2. *Quorum sensing in Gram-positive bacteria*

Gram-positive bacteria do not use the LuxI/LuxR-type signaling. In this bacterial group, QS is mediated by small autoinducing peptides called AIPs, that are detected by membrane-bound two-component signal transduction systems. These molecules have variations in the type, size, and complexity of regulatory factors according to the cell, which allow intraspecific communication [39–41].

AIPs do not freely diffuse across the plasma membrane, so bacteria secrete the signal molecule via ABC-type export proteins. These molecules are then recognized by two-component sensor kinases located in the cell membrane, transferring this information via phosphorylation to intracellular response regulators. Then, the phosphorylated regulatory protein binds to promoter regions of QS-regulated genes and alters their transcription, as indicated in Fig. 2A [18,23,39].

An example of this two-component communication system is described for *Staphylococcus aureus*. These processes are regulated by the Agr QS system, consisting of four genes that encode the expression of four proteins: (i) AgrD, which becomes the AIP; (ii) AgrB, a protein that exports AIP; (iii) AgrC, a protein that detects AIP and is the histidine kinase responsible for signal transmission; and (iv) AgrA, the transcriptional regulator (see Fig. 2A). At high cellular concentrations during invasive infection and during intracellular growth, *agr* is expressed at high levels. The concentration of AIP, produced by AgrD, gradually increases, and binds to the membrane histidine kinase receptor (AgrC), leading to phosphorylation of its cognate response regulator, AgrA. The activated AgrA binds to DNA with various effects, such as the secretion of virulence factors, allowing for production of tissue-destructive enzymes [23,39,41,42].

Other Gram-positive bacteria use similar QS systems. In addition to the virulence factors of *S. aureus*, other examples of QS-regulated behavior are the development of genetic competence in *Streptococcus pneumoniae*, sporulation in *Bacillus subtilis* and the production of bacteriocins by many species of lactic acid bacteria, including the production of nisin by *Lactococcus lactis* [18,40,43].

2.3. AI-2 mediated QS system

Autoinducer-2 (AI-2) is a QS signal that mediates communication in both Gram-negative and Gram-positive bacteria. This signal molecule mediates interspecies communication, that is, bacteria receive AI-2 released by foreign bacteria and regulate corresponding gene expression [20,44].

The AI-2 is produced from the precursor 4,5-dihydroxy-2,3-pentanedione (DPD) by the LuxS (*S*-ribosylhomocysteinase) synthase. The synthesis of DPD starts from SAM, which is converted to *S*-adenosylhomocysteine (SAH), further to *S*-ribosylhomocysteine (SRH) in the presence of specific enzymes. Then, LuxS converts SRH to DPD and homocysteine. Finally, DPD eventually undergoes cyclization converting to AI-2 molecule [8,20,45]. The molecular structure of DPD is very unstable, and cyclization and rearrangement may change at any time. Thus, a variety of AI-2 molecules with different structures, compositions, and similarities can be formed [44].

The first indication of bacteria communication between species emerged from the bioluminescent response of *Vibrio harveyi* by the addition of cell-free supernatant from other bacterial species [46]. Subsequently, the QS system in *V. harveyi* has been extensively investigated and thoroughly documented (Fig. 2B).

V. harveyi produces two autoinducers: i) HAI-1 (Harvey Autoinducer-1) is a typical AHL, but its synthesis is not dependent on a LuxI-type protein, instead it is synthesized by a LuxM/AinS type protein, and is used for intraspecies communication; and ii) AI-2, a furanosyl borate diester, used for interspecies communication. Both signals transduction occurs via a Gram-positive-like phosphorylation cascade, as observed in Fig. 2-B. At high cell densities, the LuxM protein synthesizes HAI-1, and LuxS protein synthesizes AI-2. HAI-1 and AI-2 are detected by LuxN and LuxP receptors, respectively. LuxP and LuxN contain a two-component hybrid sensor kinase region (histidine residues) and response regulator region (aspartic acid residues). Sensory information from LuxP and LuxN is transduced to LuxU (phosphotransferase protein), and LuxU communicates with downstream response regulator LuxO, which activates

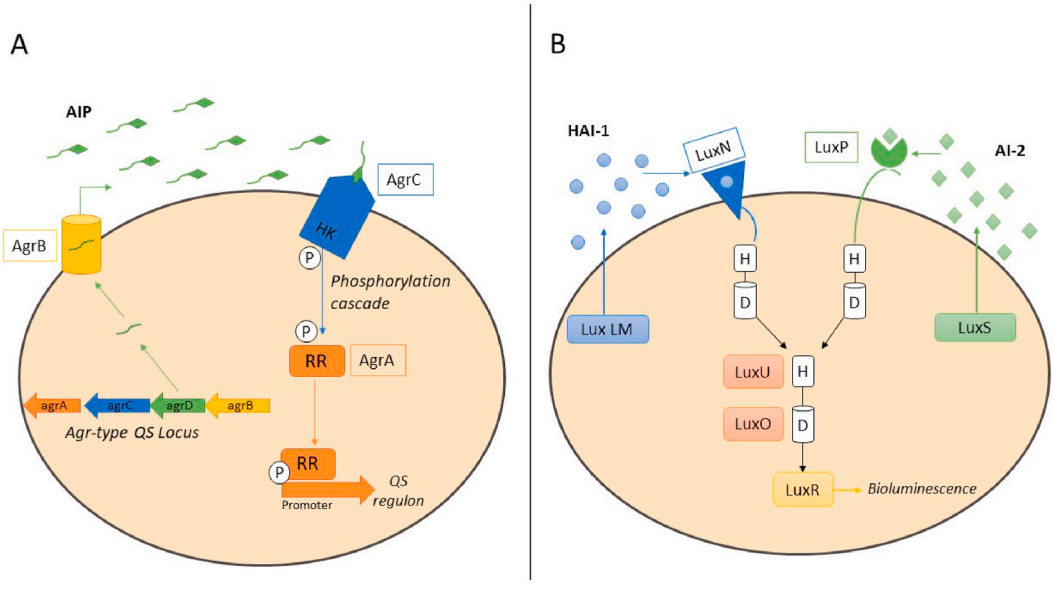

Fig. 2. Quorum sensing by two-component systems. A) Mechanism of QS in Gram-positive bacteria, particularly in *Staphylococcus aureus*. B) QS circuits in *Vibrio harveyi*. AIP, autoinducer peptides; RR, response regulator; H and D denote histidine and aspartate residues, which are phosphorylated upon signaling.

LuxR through a series of steps and results in the regulation of genes that are required for group behaviors, such as bioluminescence [8,17,45] (Fig. 2-B). Even though LuxR from *V. harveyi* has the same name, it is not homologous to LuxR type protein that detects AHLs in *A. fisheri* and in other Gram-negative bacteria [47]. Some authors call it LuxRvh to better differentiate it from typical LuxR-type proteins.

3. Targeting virulence to control bacterial infections

Bacterial pathogenicity is a complex process that involves the coordinated expression of cell components during different stages of infection. For instance, different virulence factors act in host invasion, tissue colonization and damage, and evasion of host defenses. Traditional methods to combat bacterial infections are based on interruption of cell growth (inhibition of cell wall synthesis, for example), destabilizing components of cellular membrane, inhibiting DNA replication or restricting protein synthesis [1]. The use of antibiotics has become the dominant treatment for infections [48]. Although these strategies remain effective and will continue to play a key role to treat microbial infectious diseases, the emergence of multidrug-resistant bacteria is troublesome [49].

Antibiotic resistance remains a major public health concern, particularly for the so called ESKAPE pathogens: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp., because they are pathogenic and commonly multidrug resistant microbes [50]. Strategies that should be adopted to minimize antibiotic resistance are the prudent antibiotic stewardship, the development and approval of new drugs [51], the development of fast and accurate diagnostic tools such as molecular methods [52] and effective communication from researchers and policymakers to the society [49]. Additionally, new effective strategies are urgently needed to treat infections and stop the spread of multidrug-resistant bacteria [10].

Anti-virulence approaches have been widely studied since they can disrupt a pathogen's virulence, by inhibiting the production or activity of virulence factors, but do not interfere in the pathogen's growth or viability [53,54]. Anti-virulence agents supposedly do not impose a strong selective pressure on bacteria and, therefore, should not support the emergence of antimicrobial resistance [10,55]. Another advantage of targeting virulence is that the side effects may be less severe on the beneficial bacteria of the host under treatment [53].

These strategies usually aim at (1) specific virulence factors, such as type III secretion systems (T3SS) which are directly related to pathogenicity during host cell invasion [56] or toxins; (2) master virulence regulators including QS proteins, which will be discussed below, and (3), resistance to host defenses and antibiotics [54], such as biofilm production which aids in bacterial resistance and polysaccharide capsule production, an important virulence factor for a wide range of bacterial pathogens [57]. Other recently discussed strategies include microbiome-modifying therapies such as fecal transplantation [55,58] and the employment of phages as treatment in specific situations or salvage therapy for patients with infections that have not responded to any other treatment [55].

3.1. Quorum sensing inhibition as an anti-virulence strategy

Quorum sensing disruption has been pointed out as an effective strategy to control bacterial infections [59]. This approach is not intended to kill bacteria, but instead to block the expression of multiple virulence factors, making the bacterial cells less virulent and more vulnerable to host immune responses [54,60]. The inhibition of QS signaling is also termed quorum quenching (QQ) [61,62] and compounds with this activity are called quorum sensing inhibitors (QSI), mainly natural compounds, such as phytochemicals or plant extracts as well as compounds derived from chemical libraries [63,64].

These QSI can be natural or synthetic compounds, acting as inhibitors or agonists of the signaling circuit, or enzymes that inactivate the autoinducers, or possibly monoclonal antibodies, for instance, that sequester the autoinducer and protect mice from *P. aeruginosa* infections [31]. The key advantages of using QSI include the minimal disruption on the host's commensal microbiota, rapid inactivation of the target, potential synergy with antibiotics to increase their efficacy, inhibition of the secretion of multiple virulence factors, and reduced selective pressure when compared to conventional antibiotic treatment [60]. However, the possible development of QQ resistance has already been suggested in some studies [65].

In order to minimize the evolution of resistance against QSI, a few criteria have been established for their selection. Kalia et al. [66] point out that the ideal QSIs should have low molecular mass, high specificity, no adverse effect on hosts, high stability, resistance to degradation by host metabolism and no negative influence on host microbiome. Besides, the efficacy of these compounds must be demonstrated on clinical isolates, not only in biosensor strains.

The clinical application of QSI is still developing, but a new approach of combining antibiotics with anti-QS agents has been proposed with great therapeutic potential to treat bacterial diseases [67]. These new therapies can favor health in the sense of reducing the use of antibiotics and drugs with adverse health effects. In this scenario, Hossain et al. [68] demonstrated a synergism between conventional antibiotics with different phenolic compounds against clinical strains of *E. coli.* Vipin et al. [69] also demonstrated the synergistic effect of the flavonoid quercetin with many antibiotics against biofilm-forming *P. aeruginosa* strains previously isolated from catheter associated urinary tract infection. According to these authors, the synergistic effect of quercetin is attributed to its QS inhibitory properties.

3.1.1. Specific inhibition mechanisms in AHL-mediated QS

A true quorum sensing inhibitor (QSI) should target the signaling circuit and have no effect on other bacterial systems. In AHL-mediated QS systems, QSI can act by (i) inhibition of AHL synthesis, by interacting with LuxI-type AHL synthases; (ii) degradation or inactivation of AHLs; and (iii) inhibition of autoinducer detection by LuxR-type AHL receptors, ultimately affecting QS-regulated gene expression [31,65,70], as shown in Fig. 3 and Table 1.

3.1.1.1. AHL synthesis inhibition. The first mechanism involves the suppression of autoinducer production, inhibiting either the precursor synthesis or the activity of LuxI-type synthases. AHL signals are synthesized by LuxI-type proteins from two precursors: SAM which is the amino acid substrate, while the acyl chain of AHL is derived from ACP-coupled fatty acids or CoA-aryl/aryl moieties [71]. The synthases catalyze the formation of an amide bond between the two substrates, SAM and the acyl group [72]. The enzyme subsequently catalyzes an intramolecular lactonization, releasing *S*-methyl thioadenosine (MTA) and the AHL autoinducer [73].

Some inhibitors can affect AHL synthesis in addition to inhibiting amino acid and fatty acid metabolism, which may affect other cellular functions [72]. As the precursors (SAM and acyl-ACP) are essential and ubiquitous metabolites, a complete inhibition of their synthesis will cause bacterial death, and, therefore, would not be characterized as a specific QS inhibition strategy. This is exemplified by the triclosan molecule, which limits acyl-ACP biosynthesis at sublethal concentrations, while in high level kills bacteria [65,74]. Thus, it is necessary to identify inhibitors that specifically target AHL synthesis without hindering microbial metabolism.

In contrast to the extensive research on autoinducer receptor proteins antagonists, few AHL synthase inhibitors have been discovered to date, and several are autoinducer analogs [73].

Parsek et al. [75] did one of the pioneering studies on the kinetic process of AHLs synthesis by RhlI of *P. aeruginosa*, and found that SAM analogs, reaction intermediates and/or end products (sinefungin, butyryl-SAM and 5′-methylthioadenosine - MTA) inhibit RhlI activity. Additional inhibitors targeting AHL synthesis have been identified, which like triclosan, were found to inhibit AHL synthesis by blocking the production of the precursor through inhibition of enoyl-ACP reductase (FabI) [74]. For instance, compound J8-C8, which binds to TofI protein of *Burkholderia glumae*, effectively occupies the binding site for the acyl chain of the TofI cognate substrate [76]. Besides, some natural compounds may also have this inhibitory activity. Chang et al. [77] suggested a new class of QS-inhibiting agents from natural products targeting AHL synthases, observing that tannic acid and *trans*-cinnamaldehyde efficiently inhibited AHL production by RhlI. Molecular docking analysis with LasI and EsaI (LuxI-type protein of *Pantoea stewartia*) suggested that *trans*-cinnamaldehyde binds to crucial substrate binding pocket for AHL production [77].

Recently, Inchagova et al. [78] reported the probable anti-QS mechanism of the antibiotic amikacin by inhibition of the autoinducer biosynthesis. They observed that sub-inhibitory concentrations of amikacin resulted in progressive decrease of C6-AHL accumulation in *Chromobacterium violaceum*. In another approach, Higgins et al. [73] developed inhibitors of AHL synthases by designing analogs of the transition state of the lactonization step of the enzymatic reaction. They tested the generated compounds as inhibitors of CepI, the autoinducer synthase from *Burkolderia cenocepecia* and concluded that this approach could generate a new type of inhibitor against this underdeveloped antibacterial target. Other studies by this group performed cloning, purification and enzymatic activity of RhlI from *P. aeruginosa* [79] and BmaI1 from *Burkholderia mallei* [80] to develop inhibitors against these AHL synthase enzymes.

3.1.1.2. AHL degradation or inactivation. The second mechanism, involving autoinducer blockage, can be due to enzymatic degradation, transport/exchange inhibition or sequestration of autoinducers. A large number of QQ enzymes has been discovered, which can

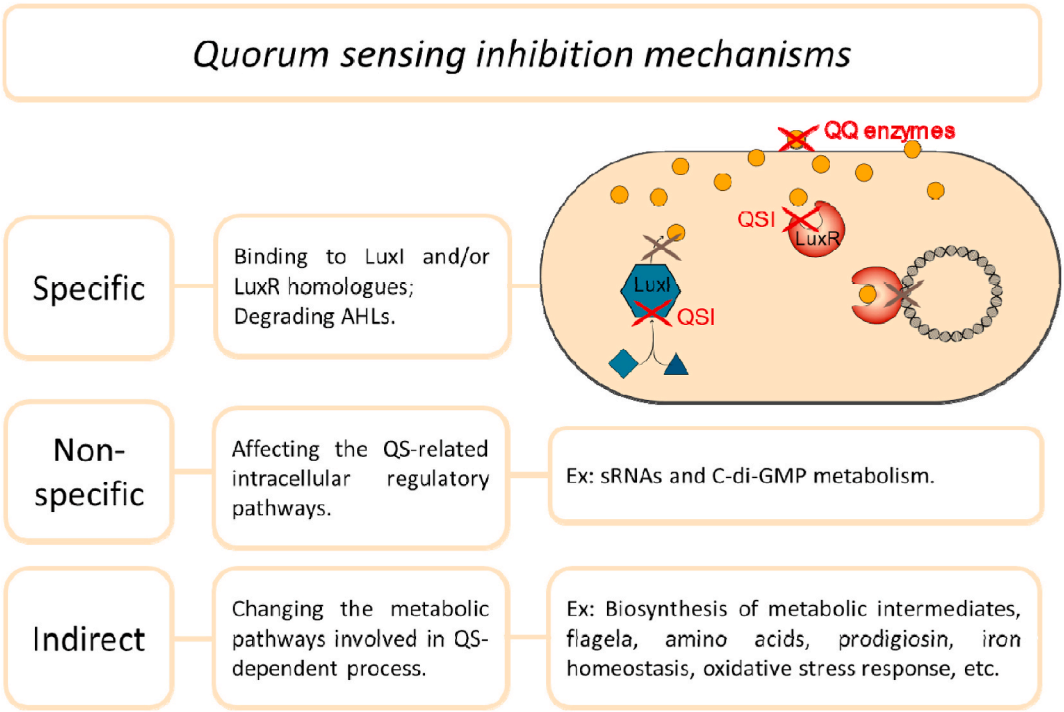

Fig. 3. Possible QS inhibitory modes of action by phytochemicals.

Table 1
Elucidated mechanisms and targets of QSI in AHL-mediated QS systems.

QS inhibitor	Mode of action	Inhibition target: protein, AHL or bacteria	Reference
Sinefungin, butyryl-SAM and MTA	AHL synthesis inhibition	RhlI protein of *P. aeruginosa.*	[75]
Compound J8-C8	AHL synthesis inhibition	TofI protein of *B. glumae.*	[76]
Tannic acid; *trans*-cinnamaldehyde	AHL synthesis inhibition	RhlI protein of *P. aeruginosa.*	[77]
Triclosan	AHL synthesis inhibition	Enoyl-ACP reductase (FabI) of *P. aeruginosa.*	[74]
Antibiotic amikacin	AHL synthesis inhibition	*CviI* of *C. violaceum.*	[78]
Thioether compound JKR-1	AHL synthesis inhibition	CepI of *B. cenocepecia.*	[73]
Lactonase AiiA from *Bacillus* sp. Strain 240B1	QQ enzyme/AHL inactivation	AHLs from *Erwinia carotovora.*	[84]
Lactonase AhlS from *Solibacillus silvestris*	QQ enzyme/AHL inactivation	C10-HSL.	[97]
Lactonase PPH from *Mycobacterium tuberculosis*	QQ enzyme/AHL inactivation	AHLs secreted by *E. amylovora* (C6-oxo-HSL).	[85]
Enzyme moLRP (marine-originated lactonase-related protein)	QQ enzyme/AHL inactivation	Low- to medium-chain AHLs, like C4-HSL and C6-oxo-HSL.	[82]
Penicillin acylase from *Streptomyces lavendulae*	QQ enzyme/AHL degradation	Long-chain AHLs, mainly C10-HSL, C12-HSL and C14-HSL.	[98]
Acylase from *Actinoplanes utahensis*	QQ enzyme/AHL degradation	Long-chain AHLs, mainly C8-HSL, C10-HSL, and C12-HSL.	[98]
Acylase APTM01 from *Pseudoalteromonas tetraodonis*	QQ enzyme/AHL degradation	Long-chain AHLs, mainly C10-HSL, C12-HSL and 3-oxo-C12-HSL.	[86]
Antibodies RS2-1G9	AHL sequestration	Inhibition of 3-oxo-C12-HSL of *P. aeruginosa.*	[87]
Analogs of 3-oxo-C12-HSL	Inhibition of response regulator	TraR protein of *Agrobacterium tumefaciens.*	[88]
Halogenated furanones	Inhibition of response regulator	Destabilization of LuxR.	[91,99]
Furanones	Inhibition of response regulator	Destabilizing LasR of *P. aeruginosa,* promoting its degradation.	[95]
Chlorolactone compound	Inhibition of response regulator	Competition with C6-HSL for binding site of CviR from *C. violaceum.*	[96]

degrade autoinducer molecules, preventing the production of virulence factors and biofilm formation [40]. The major enzymes involved in AHL inactivation include lactonases that catalyze the opening of the lactone ring, acylases which remove the acyl chain from the homoserine lactone moiety, and oxidoreductases that reduce the carbonyl moieties [81,82]. The mechanism behind the action of QQ enzymes and their potential biotechnological applications are summarized in a review by Fetzner [83].

The first lactonase identified as a QQ enzyme was the AiiA enzyme of *Bacillus* sp. Strain 240B1 [84]. Recently, Gurevich et al. [85] used enzyme-directed evolution and nanostructure encapsulation of purified lactonases to increase their thermal resistance and extend their shelf life. The authors also demonstrated that the studied lactonases successfully inhibited plant disease symptoms caused by *Erwinia amylovora* in the field, similar to the antibiotics commonly used to kill the plant pathogen. These results showed the potential of QQ enzymes in future development as antibacterial treatment. New sources of QQ enzymes have been discovered in the marine environment, such as moLRP (marine-originated lactonase-related protein) from lactonase family [82] and acylases from marine bacterium *Pseudoalteromonas tetraodonis* [86]. Regarding transport inhibition, even though most AHL signals diffuse through membranes, some molecules limit the exchange of QS signals, like antibodies, which were identified as autoinducer quenchers [65]. Kaufmann et al. [87] were pioneers in the production of AHL-sequestering antibodies, inhibiting pyocyanin biosynthesis, a QS controlled virulence factor in *P. aeruginosa,* through 3-oxo-C12-HSL sequestration. So, the production of antibodies against bacterial signaling molecules is a potential application for the development of anti-virulence strategies.

3.1.1.3. Inhibition of LuxR-type transcription regulators. Finally, the interference in LuxR-type transcriptional regulators is currently the most explored QS inhibition strategy. The current understanding is that, at some AHL threshold concentration, the AHL ligand binds its cognate receptor, a LuxR-type protein, and activates the transcription of target genes involved in group behavior [14,27]. So, blocking the endogenous AHL binding to its receptor is an attractive strategy for QS control.

Several synthetic molecules have been discovered to function as antagonists of LuxR-type proteins. Zhu et al. [88] reported that many autoinducer analogs are potent antagonists. They showed that TraR protein of *Agrobacterium tumefaciens* was strongly antagonized by analogs of the autoinducer 3-oxo-octanoyl-homoserine lactone. Geske et al. [89,90] reported an efficient synthetic route to new ligands that modulate QS, showing that synthetic non-native AHLs were potent inhibitors of QS in Gram-negative pathogens. Halogenated furanones produced by the marine red algae *Delisea pulchra* are a well-known group of anti-QS compounds [91]. Synthetic furanones, mainly (*Z*-)-4-bromo-5-(bromomethylene)-2(5*H*)-furanone (furanone C-30), are effective at reducing QS-regulated phenotypes and consequently have been used as positive control for QS inhibition in many experiments including inhibition of violacein production by *C. violaceum,* biofilm formation in *P. aeruginosa* [92] and swarming motility in *Serratia marcescens* [93]. Manefield et al. [94] revealed that furanones inhibit QS by displacing the AHL signal from its receptor protein. More recently, Paczkowski et al. [95] showed that furanones function non-competitively by destabilizing LasR protein and promoting its degradation. Unfortunately, furanones exhibit toxicity to human cells and their use is not suitable in human hosts as therapeutic agents [32,40].

Chen et al. [96] reported that synthetic molecules bind to receptor proteins and favor their inactivation. They were able to solve the crystal structure of full-length *C. violaceum* CviR with chlorolactone compound (CL), showing that it functions as an antagonist by competing with C6-HSL for the autoinducer binding site and inducing a conformational change that hinders the CviR:CL complex from binding to DNA [96].

These are some of the elucidated QS inhibitory mechanisms reported for synthetic compounds. The QS inhibitory mechanisms for natural compounds, including phenolic compounds, are still not well established, but recent studies reported that QSIs that are not structurally similar to the native AHLs, including flavonoids, may act in these regulators by many possible mechanisms including competitive inhibition, by occupying the ligand-binding site, by inhibiting protein stability, solubility or dimerization, and impairing DNA binding or RNA polymerase engagement [95].

3.1.2. Other inhibitory mechanisms

In addition to specific anti-QS strategies (via binding to LuxI/LuxR homologues), Deryabin et al. [100] proposed that plant-derived molecules can inhibit QS by two other mechanisms, namely a "non-specific" type inhibition, by affecting the QS-related intracellular regulatory pathways and an "indirect" mode, via alteration of metabolic pathways involved in QS-dependent processes (Fig. 3).

3.1.2.1. Non-specific QS-inhibitory mechanism. The non-specific QS-inhibitory mechanism was described for ajoene, a sulfur-rich molecule found in garlic, by Jakobsen et al. [101]. They revealed that ajoene mediates its anti-QS activity by lowering the expression of small regulatory RNAs (sRNA) in *P. aeruginosa* and *S. aureus*. Using various reporter constructs, they found that ajoene reduced the expression of the sRNAs RsmY and RsmZ in *P. aeruginosa* and the small dual-function regulatory RNA, RNAIII in *S. aureus*, which controls the expression of key virulence factors such as hemolysins and proteases [101]. Likewise, in a study conducted by Tan et al. [102], the QS inhibitory mechanism of iberin, an isothiocyanate compound from horseradish, is also related to lowering the expression of regulatory sRNAs RsmY and RsmZ, which in turn inhibit the expression of QS-regulated virulence factors, such as pyocyanin and protease.

The connections between QS and 3,5-cyclic diguanylic acid (c-di-GMP) have just begun to be elucidated. c-di-GMP is an important intracellular secondary messenger in bacteria that allows adaptation to different environments, including biofilm formation, motility, production of virulence factors and other behaviors [103,104]. As QS and c-di-GMP pathways regulate virulence and biofilm formation, it is presumed that they may be linked and/or intersect each other [104]. Srivastava et al. [105] had already observed this, indicating that *Vibrio cholerae* combines information conveyed by QS and c-di-GMP to respond and adapt appropriately to different environments, modulating the expression of key transcriptional regulators.

Coumarin and its derivatives, *e.g.,* aesculetin, scopoletin and umbelliferone are plant-derived compounds described as QSIs in several bacteria and the mechanism of inhibition is probably related to the reduction of c-di-GMP metabolism [100,106]. Using a transcriptomic analysis, Zhang et al. [106] demonstrated that key-QS genes (involved in the *las, rhl, pqs* and *iqs* systems) were downregulated in coumarin-treated biofilms of *P. aeruginosa*, and the expression of genes related to type III secretion and c-di-GMP metabolism were also significantly reduced in treated cells, compared to untreated controls. These results revealed that coumarin reduced both QS-regulated virulence and c-di-GMP levels. In contrast, Chua et al. [103] suggested that low c-di-GMP levels could increase expression of QS-regulated genes and the production of QS-regulated virulence factors. They observed that *P. aeruginosa* cells with high and low intracellular c-di-GMP contents possessed distinct transcriptome profiles: cells with low c-di-GMP levels induced expression of *rhl* and *pqs*-regulated virulence factors, such as pyocyanin and rhamnolipids.

Kim et al. [104] started to elucidate the relationship between QS and c-di-GMP in *P. aeruginosa* by observing the inhibitory effect of terrein, a fungal metabolite, in both QS and c-di-GMP signaling pathways. The results suggested that terrein inhibited biofilm formation by inhibition of c-di-GMP production. In addition, a supplementation of exogenous AHL reversed the inhibitory activity of terrein on c-di-GMP production, suggesting that terrein decreased c-di-GMP levels via QS signaling. Thus, there might be a strong relationship between QS and c-di-GMP production, and terrein was classified as a dual inhibitor of QS and c-di-GMP signaling [104].

Strategies that affect the QS-related intracellular regulatory pathways serve as potential targets in the development of anti-virulence therapies against pathogens that use QS-regulated virulence factors. The compounds that act by these mechanisms have an inhibitory effect on a variety of QS systems, regardless of the autoinducer nature and the signal reception [100]. However, they do not meet the high specificity criteria to be considered as an ideal QS inhibitor [66].

3.1.2.2. Indirect QS-inhibitory mechanism. The indirect mechanism has been observed for the phytochemicals vanillic acid (a benzoic acid derivative) and curcumin (a diaryl-heptanoid). These compounds inhibit the QS circuitry via alteration of metabolic pathways involved in the production of many QS-dependent virulence factors in *Serratia marcescens*, *C. violaceum* and *P. aeruginosa* [100].

The study by Sethupathy et al. [107] revealed that vanillic acid reduces virulence in *S. marcescens* by affecting the expression of proteins involved in *S*-layers, histidine, flagellin and fatty acid production. This bacterium utilizes some short-chain AHLs (C4 to C8-HSL) to regulate the expression of genes involved in biofilm formation, swarming motilities, production of prodigiosin, surfactants and extracellular virulence enzymes such as lipase, protease, and nuclease [107,108]. Thus, vanillic acid affects phenotypes related to AHL-mediated QS by altering the metabolic pathways for the production of virulence factors.

For curcumin, the proteomic, mass spectrometric and gene ontology analyses revealed that this phytochemical attenuates QS and biofilm formation in *P. aeruginosa* by targeting antioxidant enzymes, iron transport and biosynthesis of metabolic intermediates involved in the production of virulence factors [100,109]. These data suggest that the compound exhibits unusual and indirect anti-QS effect, and it can no longer be considered an exclusive QS inhibitor.

Furthermore, phenolic compounds can affect molecular targets non-specifically in microorganisms. The presence of hydroxyl groups can form hydrogen bonds and combine with enzymes, carriers, ion channels and receptors, deactivating them and consequently affecting bacterial physiology [70].

Although these compounds have an inhibitory effect on a variety of QS systems, they do not meet the specificity criteria to be considered an ideal QSI [66]. Once again, we turn our attention to the significance of QS interference in the context of human health, particularly in relation to bacterial metabolism. The metabolic pathways responsible for the synthesis of certain virulence factors in many pathogens play a vital role in their ability to cause infection within the human body, thereby directly impacting human health [110]. Consequently, inhibiting these pathways holds the potential to significantly influence bacterial infections and their consequences.

4. Updates on QS inhibition by phenolic compounds

4.1. Phenolic compounds

Phenolic compounds are plant secondary metabolites widely distributed in the plant kingdom, such as in edible fruits and vegetables. Currently, they constitute one of the most studied classes of bioactive compounds, mainly due to their bioactive properties, such as antimicrobial, antioxidant, anti-inflammatory and antiproliferative activities [4,111]. Many phenolic compounds are considered GRAS (Generally Recognized as Safe) and therefore can be safety used in industry, agriculture, and livestock [95]. Nowadays, several methodologies have been reported for the extraction of phenolic compounds from natural sources [112,113].

As for structure, phenolic compounds have an aromatic ring attached to one or more hydroxyl groups, and variations in this basic structure give an infinite number of compounds, allowing them to be classified into different categories [114,115]. One of them is according to carbon skeletons, allowing to categorize phenolic compounds into: i) compounds that contain a single aromatic ring (class C6); compounds with a benzene ring containing a carbonic side chain (class C6-Cn); or even a more complex skeleton in which the carbon chain is further linked to a second benzene ring (class C6-Cn-C6), like flavonoids [116]. The main classes of phenolic compounds are presented in Fig. 4.

Flavonoids are the majority within the class of phenolic compounds. With more than 8000 flavonoids distributed in nature, they are the most diversified compounds in the plant kingdom. They have a basic C6–C3–C6 structure, formed by two benzene rings (A and B) linked by a heterocyclic pyran ring (C) [4]. The six subdivisions of this class include flavonols, flavones, flavanones, flavanols, isoflavonoids and anthocyanidins. Non-flavonoids such as phenolic acids (simple phenols) are further divided into hydroxybenzoic acids and hydroxycinnamic acids, according to structural variations of the molecules. Tannins, stilbenes and lignans complete the category of major non-flavonoids [4,114,115]. In addition, other phenolic compounds may include capsaicinoids and curcuminoids, which, although not primarily classified as phenolics, have the basic structure of an aromatic ring linked to at least one hydroxyl (Fig. 4).

These compounds play an essential role in the balance of the plant in its natural environment and its adaptability, and their content is directly influenced by the level of stress factors in the environment. They also have a function of repelling and attracting different organisms, in addition to biological functions related to plant protection, including antimicrobial activity [111,117]. In foods, phenolic compounds contribute to sensory characteristics such as color by anthocyanins [118], astringency by tannins, besides aroma and flavor

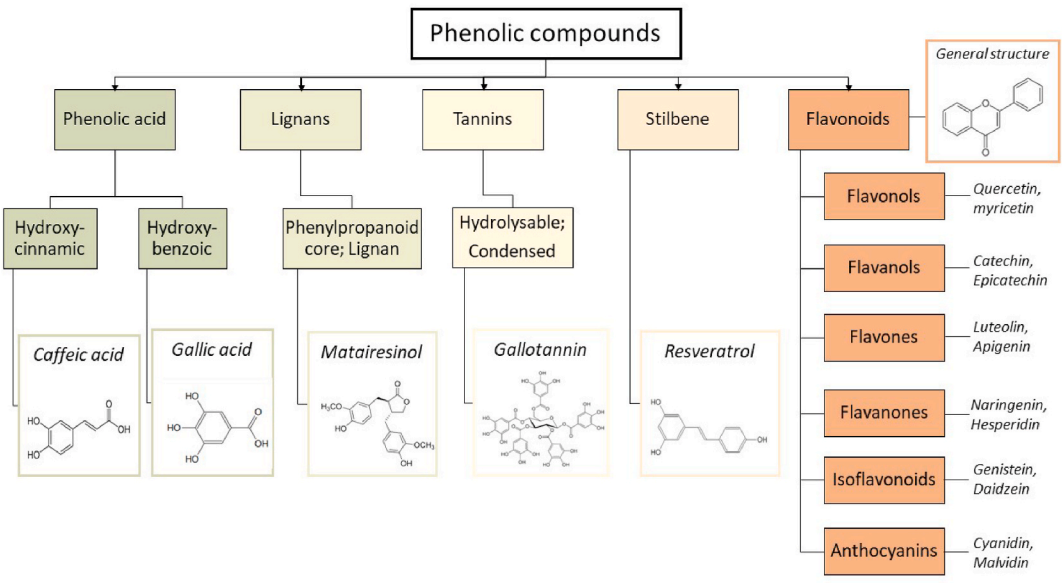

Fig. 4. Main classes of phenolic compounds and examples with chemical structure. Based on several studies, including [4,114,115].

[114,119]. When consumed, polyphenols are considered the most important antioxidants in the human diet, as they can help protect consumers against oxidative stress and promote health benefits [4,120].

4.2. QS inhibition by phenolic compounds

Recent investigations have shown that several plant-derived compounds inhibit QS-regulated phenotypes. The most studied QS inhibitory mechanism is the inactivation or competition for binding to the receptor LuxR-type proteins. Table 2 shows works published in the last five years that advanced our understanding of the QS inhibition mechanism by phenolic compounds in several bacterial strains.

When testing QSI compounds it is very important that the minimal inhibitory concentration (MIC) assay is performed reliably to ensure that the compound in study has no effect on bacterial growth. The QS dependent phenotypic assays must be performed using compounds at sub-inhibitory concentrations [59]. Otherwise, using higher concentrations, the compound may be exerting an antibacterial effect, killing the bacteria, or inhibiting their growth through different mechanisms, such as inhibition of cell wall synthesis, nucleic acid synthesis, protein synthesis, or membrane depolarization [127,128].

Additionally, as basic principles for any QS inhibitory study, it is interesting to perform tests using *in silico* studies and assays with biosensor strains, as performed for curcumin and resveratrol [122] and quercetin [93]. However, in order to characterize the specificity and the inhibition mechanism, more robust analysis should be performed with the potential compounds. For example, the molecular dynamics analysis, in which simulations in the cellular environment are performed computationally to indicate the stability of ligand receptor interactions, as performed for gingerol [123]; or gene expression assays of target QS genes, as developed for methyl gallate [70] and resveratrol [121]; or global gene expression profiles by RNA-Seq, as performed for rosmarinic acid [124]; and ultimately the specific protein:molecule interaction as developed for different flavonoids [95]. Otherwise, QS may be inhibited in a non-specific way, by lowering the expression of small regulatory RNAs, as observed by Jakobsen et al. [101] for ajoene. Or yet, phenotypes can be inhibited indirectly, by altering the regulatory pathways involved in virulence factors, as observed for vanillic acid by Sethupathy et al. [107], when carrying out proteomic analysis and mass spectrometric identification of differentially expressed proteins. In this case, the compound should not be identified as an authentic QSI.

In addition, the same compound can act by different mechanisms, depending on the bacterium, or the QS system and the analyzes being performed. For instance, curcumin has been reported as an indirect QSI [100,109], while our research group has seen compelling results with this compound through molecular docking and biosensor strains for different QS systems, suggesting a direct effect [122,129,130]. This demonstrates the need for additional studies to elucidate the inhibitory mechanism in each situation.

The inhibitory effect of flavonoids on the autoinducer-binding receptors LasR and RhlR has been validated biochemically by

Table 2
Overview of recent studies reporting probable modes of action of phenolic compounds on AHL-mediated QS in bacteria.

Phenolic compound (potential QSI)	MIC	*Anti*-QS effect (phenotypes)	Mechanism and Method	References
Resveratrol	>1000 μg/mL against *P. aeruginosa* PAO1 and clinical isolates.	Inhibition of biofilm formation and enhancement of the effects of aminoglycoside antibiotics.	Lowering expression of *lasI* and *rhlI*, analyzed by qRT-PCR.	[121]
Curcumin and resveratrol	>100 μM for *C. violaceum* ATCC 12472 and 026.	Inhibition of violacein, biofilm formation and swarming motility.	*In silico* study (docking) with CviR QS regulator of *C. violaceum.*	[122]
Gingerol	>50 μg/mL for *P. aeruginosa* AM26.	Reduced biofilm formation, exopolysaccarides (EPS), pyocyanin and rhamnolipids.	*In silico* studies - docking and molecular dynamics - with LasR, RhlR, PhzR.	[123]
Phloretin, chrysin, quercetin, baicalein.	>100 μM for *P. aeruginosa* PA14.	Suppression of virulence factors production in *P. aeruginosa.*	Allosteric inhibition of LasR/RhlR.	[95]
Methyl gallate	512 μg/mL for *P. aeruginosa* PAO1.	Reduction on biofilm formation, EPS, swarming motility, and virulence factors in *P. aeruginosa.*	Reduced expression of *lasI, lasR, rhlI,* and *rhlR.*	[70]
Vanillic acid	>250 μg/mL for *S. marcescens* MG1 and clinical isolate; >500 μg/mL for *S. marcescens* ATCC 14756.	Reduction of biofilm formation and expression of virulence factors in *S. marcescens.*	Affecting *S*-layer, flagellin and fatty acid biosynthesis proteins.	[107]
Rosmarinic acid	>100 μM for *P. aeruginosa* PAO1.	Induced the expression of 128 genes, many implicated in QS; and seven sRNAs encoded in regions close to QS-induced genes.	*In silico* study, RNA-Seq and qRT-PCR analysis.	[124]
Naringenin	>1 μM for *E. coli* LasR-based biosensor strain.	Inhibited QS-regulated virulence factors in *P. aeruginosa* PAO1.	Reduced expression of QS-regulated genes by directly binding to LasR, competing with its cognate activator (3OC12-HSL).	[125]
Chlorogenic acid	5.12 mg/mL for *P. aeruginosa* PAO1 and *C. violaceum.*	Inhibited biofilm formation, swarming and violacein production in *C. violaceum*; inhibited virulence factors in *P. aeruginosa* PAO1 and attenuated *C. elegans* killing by *P. aeruginosa.*	*In silico* study (LasR, RhlR, PqsR); reduced expression of QS-related genes (*lasI, lasR, rhlI, rhlR, pqsA, pqsR, cviI).*	[126]

Paczkowski et al. [95]. They found that nine flavonoids (phloretin, chrysin, naringenin, quercetin, baicalein, apigenin, 7,8-dihydroxyflavone, 3,5,7-trihydroxyflavone and pinocembrin) act by an allosteric mechanism, inhibiting QS in a non-competitive mechanism, *i.e.*, binding to a site on LasR/RhlR without accessing the autoinducer binding pocket. Besides, the structure-activity relationship analyses demonstrated that the presence of two hydroxyl moieties in the flavone A-ring backbone are essential for potent inhibition of the receptor proteins. These structural features can be considered for future phenolic compounds screenings.

In another study, Hernando-Amado et al. [125] observed that naringenin inhibits *P. aeruginosa* QS response through its binding to LasR by a time-dependent model of competition with its cognate 3-oxo-C12-HSL. When naringenin was added at time zero, it inhibited the expression of QS-regulated genes and virulence factors, by binding to nascent LasR. However, when naringenin was added at stationary growth phase, the QS response was not inhibited, since LasR had already been activated by 3-oxo-C12-HSL. Finally, these findings highlight the importance of searching for QSI that not only inhibit general virulence phenotypes, but that are also effective on dense populations.

Despite great advances in our understanding of bacterial communication mechanisms and the various inhibition strategies that are possible, there is a great need for the development of biotechnological applications for these inhibitors in real life scenarios, including clinical trials, in order to show their efficacy in treating bacterial infections, and challenge tests related to controlling bacterial spoilage processes in foods.

5. Conclusions

Recent investigations have shown that several plant-derived compounds inhibit QS-regulated phenotypes. We concluded that phenolic compounds can inhibit these phenotypes by various mechanisms, including the disturbance in the specific signaling circuit and alteration in the regulatory and metabolic pathways. We have observed that the expression of these phenotypes depends on several factors, including QS, but not restricted to it. In addition, the same compound can act by different mechanisms, depending on the bacterium, or the QS system and the analyzes being performed.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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