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Medicinal plant products targeting quorum sensing for combating bacterial infections

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ABSTRACT

Traditional treatment of infectious diseases is based on compounds that aim to kill or inhibit bacterial growth. The bacterial resistance against antibiotics is a serious issue for public health. Today, new therapeutic targets other than the bacterial wall were deciphered. Quorum sensing or bacterial pheromones are molecules called auto-inducer secreted by bacteria to regulate some functions such as antibiotic resistance and biofilms formation. This therapeutic target is well-studied worldwide, nevertheless the scientific data are not updated and only recent researches started to look into its potential as a target to fight against infectious diseases. A major concern with this approach is the frequently observed development of resistance to antimicrobial compounds. Therefore, this paper aims to provide a current overview of the quorum sensing system in bacteria by revealing their implication in biofilms formation and the development of antibiotic resistance, and an update on their importance as a potential target for natural substances.

1. Introduction

Through natural evolution, organisms have developed several sophisticated means to interact with and adapt to the environment they inhabit. Therefore, they must change their phenotypes in order to respond to different situations of extrinsic and/or intrinsic stress. They also have to change their metabolisms and other activities in order to succeed in the new environment [1].

Higher organisms have developed specific regulatory mechanisms, in which they modify their phenotypes to respond to a new situation. This modification consists of a change of their gene expression by activating or repressing the transcription factors *via* the various epigenetic changes related to DNA and/or chromatin status [2].

In bacteria, the mode of regulation of gene expression was assumed by Jacob and Monod to be only related to concerted mechanisms and other inducements. Over the last few decades, it has become clear that bacteria coordinate interactions between them on one hand and with higher organisms on the other hand by an intercellular communication system that is often based on the expression of new genes, called quorum sensing (QS) system [3,4]. QS is a system of stimuli and responses in relation to bacterial cell population density that regulates gene expression, including virulence determinants. This system regulates a number of activities in bacteria, including pathogenicity and antibiotic resistance. The QS participates in the formation of microbial biofilms, which are the cause of resistance to antibiotics and possibly to chronic infections. Moreover, the mechanistic understanding of the QS could be exploited to specifically counteract the formation of biofilms and possibly the resistance developed by the bacteria they form. The inhibition of QS molecules requires the specific screening of several molecules of various chemical natures. More recently, some studies have proved the anti-QS properties of natural herbal medicinal substances.

Due to their large diversity and biochemical complexity, natural products act in different ways against QS mediators and inhibit the formation of biofilms. Herein we give an overview of QS, we discuss the QS system, its recently discovered role in pathogenicity through the formation of biofilms and the development of antibiotic resistance. Then, we apprehend the anti-QS properties of natural substances to counteract the emergence and re-emergence of infectious diseases.

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2. Overview on QS

The QS is a mode of bacterial signaling that is based on the production during the bacterial growth phase of small mediating molecules called "auto-inductors". When a concentration threshold is reached, these auto-inductors interact with a transcriptional regulator, allowing the specific expression of a group of genes, in response to a high concentration of this auto-inducer. One of the most studied intra-species auto-inducers is N-acyl homoserine lactone (AHL) in Gram-negative bacteria. In these bacteria, the QS genetic determinants are organized into a complex regulatory network including the QS cascade and a spectrum of transcriptional and post-transcriptional regulators that affect the synthesis of the AHL auto-inducer. There are over 70 species of Gram-negative bacteria known to use AHL as a signaling molecule (Figure 1) [5,6]. Gram-positive bacteria use oligopeptide-based signaling with a two-component sensor. Apart from the lactones, Gram-negative and Gram-positive bacteria can also use a common signaling molecule (borate furanosyl), known as auto-inducer-2 (IA-2) and (IA-3) (Figure 2) [7,8].

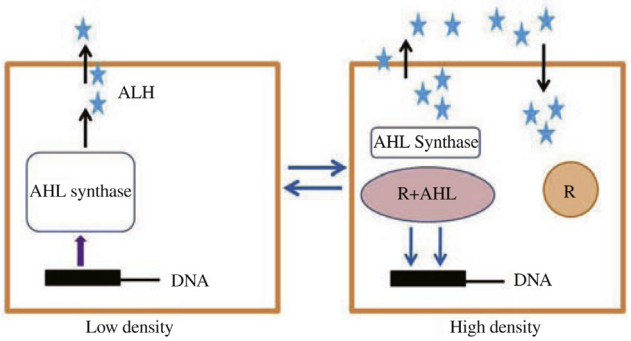

Figure 1. Quorum sensing in Gram-negative bacteria.
The bacteria produce an autoinducer, AHL, by AHL-synthase. At low density, AHL molecules are actively transported from the external environment to the cytoplasm by an ATP-dependent transport process. At high concentration, transport is carried out by passive diffusion. When the concentration of AHL reaches a threshold (Quorum State), the autoinducer molecules of AHL interact with a regulatory protein R, usually known as transcriptional regulator. The R-AHL complex binds to the promoter of the target genes and initiates their transcription coupled to the bacterial density.

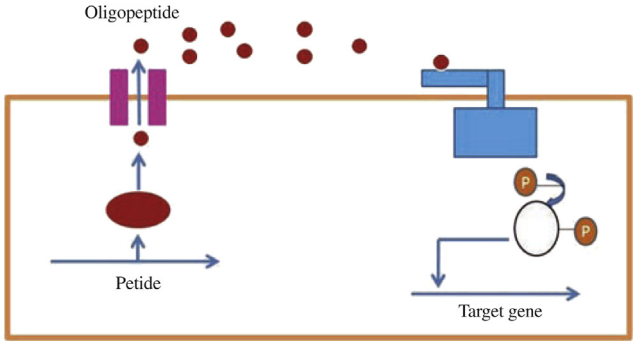

Figure 2. Quorum sensing in Gram-positive bacteria.
Autoinducers of Gram-positive bacteria are oligopeptide which are most often post-translationally modified by the addition of lactone or thiolactone, lanthionine and isoprenyl. These autoinducers oligopeptide are detected by transmembrane proteins transducing the signals by a phosphorylation cascade. The variations are recognized by the two-component receivers and ensure the specificity of the signal.

3. QS signaling pathways

3.1. QS based on AHL molecules

In Gram-negative bacteria such as *Pseudomonas aeruginosa* (*P. aeruginosa*), the LasR-I and RHLR-I systems are involved in the QS process [9]. The synthesis of AHL molecules is catalyzed by a specific enzyme called lactone synthase (as luxI). This enzyme is secreted into the extracellular medium [9]. As the cell density increases (reach quorum), the AHL present in the medium reaches a critical concentration and during this phase the AHLs diffuse into the cell and then interact with the transcription regulators. In *P. aeruginosa*, there is the production of two AHL molecules form, 3OC12-HSL and C4-HSL. Each molecule is binding to their transcriptional regulator (LasR to 3OC12-HSL and RHLR to C4-HSL) [9]. These formed complexes may furthermore activate numerous transcription regulators such as lasI, lasB and toxA [10]. The activation of a family genes regulator is related to the concentration of AHL molecules (Figure 1).

3.2. QS based on peptide secretion

The QS molecules in the Gram-positive bacteria are based on the formation of the oligopeptide from the peptide (Figure 2). These molecules called auto-inducing oligopeptide (AIPs) are used QS sensing signaling molecules (AIPs). These AIPs are secreted into extracellular and have an affinity to the histidine membrane receptor kinases [11]. The expression of AIPs peptide molecules is related to the agrD gene family. Once expressed, the membrane-bound AgrB protein modifies their confirmation by addition of thiolactone and thus they can be exported to the extracellular media as oligopeptide [12]. When the extracellular concentration of AIPs reaches a threshold, these molecules can be bound to the AgrC receptor (membrane-bound receptor kinase). The transmembrane signal transduction generates the auto-phosphorylation AgrA thus activating several signalization pathways that are responsible for the agrBDCA protein expression [13]. The activation of this system depends on cell density concentration. When the cell density increases, the agr system will be activated thus switching the bacterial physiological states on the toxin and protease secretions depending on the cases such as the adhesion, the commensalism, invasion and then the aggression [14,15].

3.3. QS based on production of AI-2 system

This system is found in the Gram-negative bacteria and Gram-positive bacteria. It is based on a signaling molecule called furanosyl borate diester (AI-2). This molecule switches between the inter- and intra-species signal depending on the threshold concentration and cell density [15]. It is found in several pathogenic bacteria, such as *Vibrio harveyi* (*V. harveyi*, the first strain that AI-2 signaling molecules were reported), *Streptococcus gordonii* and *Salmonella typhimurium* [15]. These molecules are synthesized by Al-2 synthase in all the bacteria that it uses. However, they can use it in signal transduction to smell and serve a variety of bacteria in their surrounding environment. In *Salmonella typhimurium*, the AI-2 system is regulated by the luxS-regulated operon and the synthesis of Al-2 is performed by luxS (metalloenzyme) from a

precursor molecule called: S-adenosyl homocysteine [16]. As with other self-inductive molecules, the AI-2 protein is also worked into the cells *via* specific transporters. Once inside the cell, the AI-2 undergoes phosphorylation and generates a signaling pathway that ends up regulating the luxS-regulated Operon [14].

3.4. QS based on production of other system

A natural variation of the QS system is also observed. Indeed, some bacterial strains do not produce self-inductors, but respond to the signals produced by the auto-inducers of other bacteria. For example, *Escherichia coli* (*E. coli*) possesses a signal molecule called SdiA (molecule homolohue to LuxR) in response to signals from other bacteria. In addition, *Burkholderia cepacia* has been shown to respond to QS signals produced by *P. aeruginosa via* CF signal molecules [17].

4. Biofilms formation and microbial pathogenicity

Biofilm is a community of microorganisms attached to a surface and maintained by the secretion of an adhesive and protective matrix [18]. The biofilms concern the animal, vegetable, mineral, aquatic and technological world. Indeed, it is a living and dynamic structure, in perpetual alteration [19]. Their effect is often perceived as deleterious because the medical and technological aspects are brought to the foreground. However, they also have positive effects. On a global scale, the biofilm is probably the dominant way of life of bacteria. The structure and physiology of the biofilm give to the microorganisms that constitute it the conditions of social organization close to those established between the eukaryotic cells within the tissues [20,21].

Two criteria are essential in the formation of biofilm. The contextual criterion is a constituent of a mono or polymicrobial community at the level of a solid surface, including in medicine the foreign bodies (prostheses, artificial valves, catheters), on which it acquires a three-dimensional structure (sessile bacteria). While, the morphological criterion (descriptive) is associated with the formation by the concerned microorganisms of an extracellular matrix consisting of complex polymers: Extracellular polymeric substance (EPS). There is another molecular criterion that remains poorly defined because of the difficulties found in the establishment of signatures, in particular a transcriptional signature, due to the heterogeneity of the physiological state of the constitutive bacteria (alternations of variations over the time and space) [22].

In the initial stage of biofilm formation, planktonic cells cling to an appropriate surface (inert or living tissue, or artificial devices) for fixation [23]. Once the bacteria are attached to the surface, they go into the rest state. The cells then use motility for their movement. In this situation, some bacteria genes linked to the synthesis of EPS and alginate (algC) are subject to positive regulation [24]. The micro-colonies form, resulting in the formation of a differentiated cluster (biofilm) [25].

During the maturation of biofilm, the bacteria attached to the surface create a protective environment around them by secreting the EPS thus preventing the entry of antibiotics into the biofilm. They also form water channels inside biofilm to facilitate the exchange of nutrients and waste [25]. The low concentration of oxygen and nutrition within biofilm relative to the surface of peripheral cell growth faster compared to cells in the biofilm core [25]. However, the cells residing in the biofilm become tolerant and express more the virulence factors under these conditions. Moreover, when the conditions become favorable again, the cells can detach themselves from the biofilms thanks to an enzymatic staining system; Alginate lyase [26].

Several bacterial species forming the biofilm have been found to be associated with a number of human diseases [27]. In addition to infecting live tissue, many bacterial species are known to colonize catheters and form biofilms, thus causing unnecessary complications in patient care. This phenomenon is considered to be one of the most common causes of blood-borne infections associated with health care [28]. Amongst the various infections associated with the original catheters, the complication resulting from the crystalline biofilms of *Proteus mirabilis* is considered the most problematic because they are known to initiate pyelonephritis and septicemia [29].

The formation of biofilms is an average for developing resistance. When bacteria engage in biofilm growth mode, they can have two consequences: recalcitrance to antibiotics and persistence immune system defense. Some bacteria tolerate concentrations of antibiotics from 10 to 1 000 times higher than minimum inhibitory concentration (MICs) of genetically similar bacteria grown under planktonic conditions. This resistance is due to the development of various strategies of subversion against antibiotics: 1) decreased accessibility of antibiotics by the biofilm matrix, 2) increased activity of effluent pumps (Multidrug efflux pumps), 3) A state of metabolic heterogeneity, particularly of slow growth or even dormancy of bacteria in some sectors of the biofilm, 4) expression of genes involved in the general response to stress, 5) Emergence of a phenotype specific to bacteria in biofilm, 6) genetic switching regulating the passage of planktonic bacteria to persistent bacteria and the likely combination of several of these factors.

Other bacteria, when they engage in biofilm growth mode, acquire subversive immune defense capabilities. The mechanisms involved are: 1) limitation of the penetration of phagocytic cells (PNN) into biofilms and prevention of the diffusion of their bactericidal molecules, 2) the establishment of a program of resistance to phagocytes and their bactericidal effectors (regulation *via* feedback between the secreted peptides and their extracellular receptors) and QS mediators (3) inhibition of the phagocytic properties of the cells recruited by the EPS of the biofilm), 4) inhibition of the bactericidal properties of PNN effectors by concentrated molecules in the biofilm matrix, 5) blocking access of the antibodies to the bacteria present in the biofilm. In some cases, the situation becomes more aggravating when we have a metabolic heterogeneity mainly due to the accumulation of multiple micro-niches in private areas of nutrients where bacteria are a phenotype “dormant” in stationary phase. This heterogeneity probably largely involved with recalcitrance and persistence properties [21].

5. Implicating of QS in biofilm formation

When the bacterial population reaches a quorum, cell-to-cell communication is established by several chemical signaling molecules (auto-inducers) which, at a minimum threshold concentration, can affect genes expression. As bacteria develop, they communicate with one another using these signals and the

process is known as QS [30]. Different microorganisms are known to use QS for the regulation of antibiotic production, virulence, bioluminescence, motility, symbiosis and biofilm formation [30]. When QS signaling molecules reach an optimal concentration, these chemicals diffuse into the cell and regulate genes expression of some proteins that coordinate their behavior in a group-based manner (bacterial colonization and biofilm formation) [31].

Several studies have shown the involvement of QS intercellular signals in the different phases of biofilms formation [13,32]. For example, the biofilm formation in *P. aeruginosa* goes through several stages, in each stage, control of the bacteria population growth induced by the initial adhesion is relayed by the QS system [19]. The biofilm matrix consists largely of EPS and its production is also under the control of QS. The nature of the EPS varies between bacterial strains [18,33]. For example, in the Gram-positive bacteria such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, the EPS is essentially cationic [18]. While, on Gram-negative bacteria such as *E. coli*, the EPS are neutral or polyanionic, this strain produces the cellulose as an essential component of their biofilms [34]. Besides, pathogenicity of bacteria and their ability to form biofilms are increasingly aggravating when their cell density is high [35]. This characteristic is related to the presence of other bacterial species and the cell-to-cell interaction influences the ability of each species to produce QS signals [36].

6. QS as targeting therapeutic pathway to combat bacterial pathogenicity

The emergence of antibiotic resistance is an insurmountable problem, which necessitates the development of new therapeutic approaches to combat this global problem [37]. One of the most effective approaches today is to target QS mediators to counter the emergence and reemergence of infectious bacterial diseases [38]. New anti-QS molecules are now being considered as a useful alternative to overcome the enormous challenge posed by drug-resistant pathogens (antibiotics). Several strategies have been considered to interrupt and or disrupt the bacterial QS system. They include: Inhibition of signal generation, inhibition of signal diffusion, and inhibition of signal reception (Figures 3 and 4).

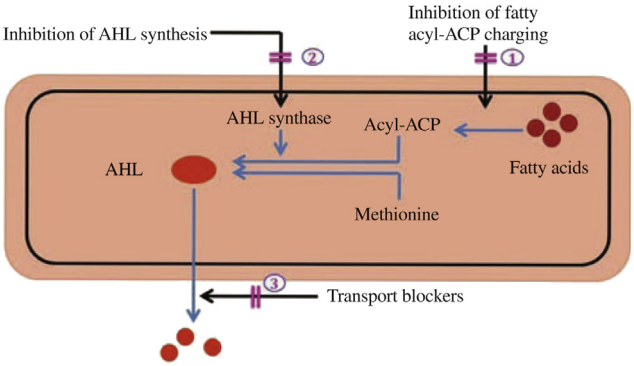

Figure 3. Inhibition of quorum sensing signaling by inhibition of AHL signal generation.
There are three mechanisms: 1) Inhibitors that affect the synthesis of fatty acyl-acyl carrier protein (acyl-ACPs; one of the substrates for the AHL synthase), 2) Direct inhibition of N-acyl homoserine lactone (AHL) synthesis and 3) Inhibition of the HLAs transport.

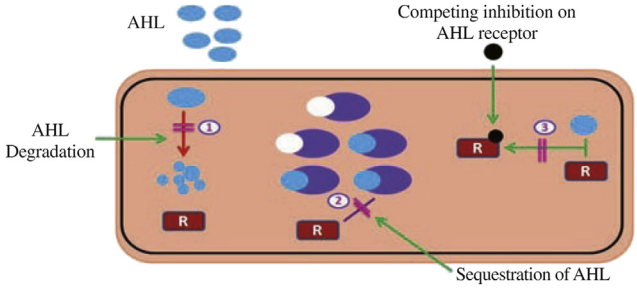

Figure 4. Mechanisms of action against quorum sensing affecting the signal reception.
There are three fundamental mechanisms inhibiting quorum sensing signal reception: 1) Signal turnover by AHL degradation, 2) Sequestration of AHL signaling pathways and 3) competition on AHL receptor AHL-mimetic compounds.

7. Inhibition of QS by bioactive compounds

7.1. Chemical compositions of medicinal plants

The number of natural substances with proven biological properties is constantly increasing and this category of molecules has now representatives in most chemical classes of the plant genus: polyphenols, terpenes, alkaloids, and coumarins.

7.1.1. Phenolic compounds

Polyphenols or phenolic compounds are molecules synthesized by plants. They belong to their secondary metabolism and participate in their defense against environmental aggressions. These are phytomicronutrients and usually pigments responsible for the hues of the leaves and colors and fruits. Phenolic compounds form the most important group of phytochemicals in plants [39]. It is a class made up of about 8 000 compounds, all of which have one thing in common: the presence in their structure of at least one aromatic ring with six carbons. It is divided into at least 10 different classes according to their basic chemical structure, and can range from simple molecules such as phenolic acids to highly polymerized compounds such as tannins [40]. Polyphenols can thus reduce or block many mechanisms involved in the genesis or amplification of certain pathologies such as cancers and cardiovascular diseases.

7.1.2. Phenolic acids

A phenolic acid is an organic compound having at least one carboxylic function and one phenolic hydroxyl. In plants, these acid phenols are often in the form of esters of aliphatic alcohols or esters of quininic acid, rosmarinic acid or glycosides. The sites and the number of the hydroxyl groups of the phenolic group have a close relationship with the toxicity towards the microorganisms: the more the hydroxylation increases, the greater the toxicity. The mechanisms responsible for phenolic toxicity against microorganisms including enzyme inhibition by oxidized compounds may result from reactions with sulfhydric groups or non-specific interactions with proteins [41].

7.1.3. Flavonoids

The term flavonoid refers to a very wide range of natural compounds belonging to the polyphenol family. Nowadays, more than 4 000 flavonoids have been identified. They have a

common biosynthetic origin and therefore all possess the same basic skeleton with fifteen carbon atoms, consisting of two aromatic units, two C_6 rings linked by a C_3 chain [42]. Structurally, flavonoids are divided into several classes of molecules according to the degree of oxidation and the nature of the substituent carried on the cycle. C_{14} different groups have been identified from which six groups are particularly the most answered and best characterized: Flavones, isoflavones, flavanones, flavanols, flavonols and anthocyanidins [42,43].

Their biosynthesis is carried out starting from a common precursor, 4,2′,4′,6′-tetrahydroxychalcone. This yellow chalcone is metabolized, under the action of the enzyme chalcone isomerase, into flavanone (naringenin). This is followed by flavone synthase or (2S)-flavanone-3-hydroxylase to form the flavone (apigenin) or dihydroflavonol. The two enzymes focus in different ways; the first introduces the double bond between the C_2 and C_3 carbons, while the second catalyzes the hydroxylation of the C_3 carbon. Dihydroflavonol, in the presence of flavonol synthase or sihydroflavonol-4-reductase is metabolized to flavonol (kaempferol) or flavan-3,4-diol (leucoanthocyanidol). The latter appears to be the precursor of flavan-3-ols and anthocyanidols. Pelargonidol, under the action of 3-*O*-glycosyltransferase, is transformed into anthocyanoside (pelargonidol-3-glycoside). The compounds of each subclass are distinguished by the number, position and nature of the substituent (hydroxyl groups, methoxyl groups and the like) on the two aromatic rings A and B and the intermediate C_3 chain [44].

Flavonoids are the pigments responsible for the coloring of flowers, fruits and leaves. Flavonoids show interesting properties in controlling plant growth and development by interacting in a complex manner with the various plant growth hormones [45]. Some of them also play a role of phytoalexin, that is to say metabolites that the plant synthesizes in large quantities to fight against some infections caused by fungi or bacteria. Moreover, flavonoids have an important therapeutic interest thanks to their various biological properties such as anticancer, antiviral, antibacterial, anti-inflammatory and antioxidant activities [46–60].

7.1.4. Terpenes

Terpenes are naturally occurring hydrocarbons of either cyclic or open chain structure: their crude formula is $(C_5H_X)_n$ where x is a variable in relation to the degree of unsaturation of the molecule and n can take values from 1 to 8 except in polyterpenes where it can reach more than 100. The basic molecule is isoprene of formula C_5H_8. The term terpenoid refers to a set of substances presenting the terpene skeleton with one or more chemical functions (alcohol, aldehyde, ketone, acid, lactone, *etc*.). Their classification is based on the number of repetitions of the isoprene base unit: hemiterpens (C_{30}), tetratepens (C_{40}) and polyterpens.

Since antiquity, certain characteristics and biological functions of terpenes were known to humans and these have been used indirectly by the use of spices as perfumes and preservatives [49,61]. Later, the research on the active compounds resulted in the extraction of volatile terpenes from the plants. These plant extracts whose major components are mono and sesquiterpenes are called essential oils. HEs are aromatic liquids obtained from different parts of plants most often by the distillation method. The oils and their compounds have shown several pharmacological activities such as antitumor, antiviral, antibacterial, antifungal, anti-inflammatory, anti-parasitic and antioxidant properties [62–65].

7.2. Medicinal plants QS inhibitors

The secondary metabolites of medicinal plants such as terpenoids and flavonoids are shown to be effective against pathogenic bacteria even at low concentrations [66]. The mechanisms of action of these products have been suggested against numerous bacterial targets including the membrane, the wall and the respiratory chain [67,68]. The molecular bases of such mechanisms are related to the terpenoids and phenols present in these products. Moreover, the organic extracts also showed very promising antibacterial properties correlated with the contents of phenolic compounds such as flavonoids [48].

Therefore, the bacteria resistant to these agents have oriented research towards the action of these substances against the QS to limit this resistance. The results of several studies suggest that the targeting of anti-QS molecules could be a new effective strategy for fighting infections *via* biofilms [69]. Phytomolecules are also capable of inhibiting the QS processes linked to human pathogens [70–72], which is a particularly attractive property.

For these reasons, researchers are increasingly focusing their studies on medicinal herbal products to identify novel therapeutic and antipathogenic agents that could act as non-toxic QS inhibitors, thus controlling infections without encouraging the development of bacterial resistance [38]. On the other hand, phytochemicals may represent the richest available reservoir of new therapeutic products [73].

Medicinal substances are present in the whole plants or in one of their particular organs (leaves, flowers, roots and seeds). The most common plants in discussed area are *Glycyrrhiza glabra* [74], *Termanilia chebula* [75], *Psoralea corylifolia* [76], *Piper bredemeyeri* [77], *Syzygium aromaticum* [78], *Bauhinia acuruana*, *Pityrocarpa moniliformis*, *Commiphora leptophloeos* [79], *Cocos nucifera* [80] and *Terminalia catappa* [81]. Table 1 represents medicinal plants that have been used as anti-QS agents with type of extracts and major compounds.

These and other medicinal plants contain several bio-active molecules such as terpenoids, polyphenols, flavonoids, tannins and anthocyanins, polyamines, cytokinins and polysaccharides that can be useful severely to counterbalance the bacteria resistance by targeting QS signaling pathways [82–88]. Table 2 shows a list of bioactive molecules extracted and isolated from medicinal plants that directly inhibit QS (Table 3).

Essential oils from medicinal plants such as *Citrus reticulate* [89], *Eucalyptus radiate*, *Eucalyptus globulus* [90] and *Thymus vulgar* [91] have shown anti-QS effects. Organic extracts from some medicinal plants such as *Rubus rosaefolius* [92], *Centella asiatica* [93], *Areca catechu* [94], and *Sclerocarya birrea* [95] have also been shown to have an inhibitory effect against QS signaling.

However, the anti-QS activity of medicinal plant products (extracts and essential oils) is still poorly understood and it is very likely that the antimicrobial efficacy will be mediated by QS inhibition. The mechanisms could be due to the effects of major components in these products, synergistic effects between majority chemotypes and minor components have an additive effect in some types of mechanisms.

Until now, numerous molecules that can inhibit QS mediators by different mechanisms have been identified and isolated from medicinal plants [75,85,96–98]. These molecules have a

Table 1

Anti-quorum activity of some medicinal plants extracts and essential oils.

Plant species (family)	Products	Major compounds	Strains tested	Effects	References
Glycyrrhiza glabra (Fabaceae)	Methanol extract	Flavonoids (Licoricone, glycyrin, gylzyrin)	*Acinetobacter baumannii*	Diminution of biofilms formation and motility. Reduction of QS molecules regulating virulence factors.	[74]
Terminalia chebula (Combretaceae)	Fruit extract	Ellagic acid (Benzoic acid)	*Burkholderia cepacia*	Reduction of biofilms formation.	[75]
Piper bredemeyeri, *Piper Brachypodom*, and *Piper bogotence* (Piperaceae)	Essential oil	ND	*Chromobacterium violaceum*	Inhibition of violacein production.	[77]
Commiphora leptophloeos (Burseraceae)	Extract (stem bark)	ND	*Staphylococcus epidermidis*	Inhibition of QS factors controlling biofilms formation.	[79]
Pityrocarpa moniliformis (Leguminosae)	Extract (leaves)	ND	*Staphylococcus epidermidis*	Inhibition of QS factors controlling biofilms formation.	[79]
Bauhinia acuruana (Leguminosae)	Extract (branches, fruits)	ND	*Staphylococcus epidermidis*	Inhibition of QS factors controlling biofilms formation.	[79]
Cocos nucifera Linn. (Arecaceae)	Husk fiber extract	ND	*Pseudomonas* sp., *Alteromonas* sp., and *Gallionella* sp.	Inhibition of biofilms formation and EPS production	[80]
Terminalia catappa (Combretaceae)	Methanolic extract (leaf)	ND	*Chromobacterium violaceum* and *Pseudomonas aeruginosa*	Inhibition of QS controlled violacein production. Inhibition of biofilms maturation.	[81]
Terminalia catappa (Combretaceae)	Methanol extract	ND	*Chromobacterium violaceum* and *Pseudomonas aeruginosa*	Inhibition of violacein production in *C. violaceum*. Reduction of LasA activity production and inhibition of biofilms maturation in *P. aeruginosa*.	[81]
Citrus reticulata (Rutaceae)	Essential oils	Limonene	*Pseudomonas aeruginosa*	Inhibition of biofilms formation at 0.1 mg/mL. Inhibition of biofilm cell viability (41%) and AHL production (33%).	[89]
Eucalyptus radiate (Myrtaceae)	Essential oils	Limonene; α-terpineol; α-terpinyl acetate; α-pinene	*Acinetobacter baumannii*	Inhibition QS-regulated violacein pigment production in bacteria.	[90]
Eucalyptus globulus (Myrtaceae)	Essential oils	1,8-cineole (Eucalyptol); α-pinene; Aromadendrene; *p*-cymene	*Acinetobacter baumannii*	Inhibition of QS-regulated violacein pigment production in bacteria.	[91]
Thymus vulgare (Lamiaceae)	Essential oils	Carvacrol Thymol	*Pseudomonas fluorescens* KM121	Significant diminution of AHLs production in 72-h-old. Significant suppression of bacteria motility and reduction of mRNA flagella gene production.	[91]
Rubus rosaefolius (Rosaceae)	Phenolic extracts	ND	*Chromobacterium violaceum*, *Aeromona hydrophila* and *Serratia marcescens*	Inhibition of some phenotypes typically regulated by QS in bacteria such as violacein production, swarming motility and biofilms formation.	[92]
Centella asiatica (Apiaceae)	Flavonoid rich fraction	ND	*Pseudomonas aeruginosa* PAO1 and *Chromobacterium violaceum* ATCC12472	Inhibition of violacein production in *C. violaceum* at 400 mg/mL. Inhibition of QS-regulated phenotypes such as pyocyanin production, elastolytic and proteolytic activities, swarming motility, and biofilms formation in *P. aeruginosa* PAO1 in a concentration-dependent manner.	[93]

Areca catechu (Aricaceae)	Extract (seed)	ND	*Chromobacterium violaceum* and *Pseudomonas aeruginosa*	Interference with violacein production and swarming motility.	[94]
Sclerocarya birrea (Anacardiaceae)	Methanolic extract (stem bark)	ND	*Pseudomonas aeruginosa*	Reduction of swimming, motility and virulence factors production.	[95]
Ocimum sanctum (Lamiaceae) *Ananas comosus* (Bromeliaceae) *Musa paradiciaca* (Musaceae) *Manilkara zapota* (Sapotaceae)	Aqueous extracts	ND	*Chromobacterium violaceum* and *Pseudomonas aeruginosa*	Inhibition of AHL-mediated violacein production in *C. violaceum*. Inhibition of pyocyanin pigment, protease, elastase production and biofilm formation in *P. aeruginosa.*	[99]
Rosa rugosa (Rosaceae)	Polyphenolic extract	Epigallocatechin gallate; Epicatechin	*Chromobacterium violaceum, Escherichia coli* K12 and *Pseudomonas aeruginosa* PAO1	Reduction of violacein production in *C. violaceum*. Inhibition of swarming motility and biofilm formation in *E. coli* and *P. aeruginosa*.	[119]
Panax notoginseng (Araliaceae)	Extract (flower and root)	ND	*Chromobacterium violaceum* and *Pseudomonas aeruginosa*	Interference with violacein production and swarming motility. suppression of LasA and LasB production Down-regulation of AHLs molecules production.	[94,138]
Buchanania lanzan Spreng (Anacardiaceae)	Methanolic extract (root)	ND	*Escherichia coli* and *Pseudomonas aeruginosa*	Reduction of biofilms formation.	[139]
Syzygium aromaticum (Myrtaceae)	Essential oils	ND	*Pseudomonas aeruginosa* and *Aeromonas hydrophila*	Reduction of Las- and Rhl regulating virulence factors such as protease, chitinase, and pyocyanin production, swimming motility.	[78,140]
Psoralea corylifolia (Fabaceae)	Grape fruit juice and extract	ND	*Escherichia coli*	Inhibition of biofilms formation.	[76]
Amomum tsaoko (Zingiberaceae)	Ethanol extract	ND	*S. Typhimurium, S. aureus* and *P. aeruginosa*	Diminution of biofilm formation.	[141]
Vernonia blumeoides (Asteraceae)	hexane, dichloromethane, ethyl acetate and methanol extracts	-2-(octadeca-9Z, 12Z-dienyloxy); -bufa-20,22-dienolide, catechol; -3,5-stigmastadien-7-one	*Chromobacterium violaceum* and *Agrobacterium tumefaciens*	Ethyl acetate extract has Inhibited the violacein production and signal synthesis in tested bacteria.	[142]
Nymphaea tetragona (Nymphaeaceae)	Aqueous extract	ND	*Chromobacterium violaceum* and *Pseudomonas* aeruginosa	Inhibition of violacein production by in *C. violaceum*. Inhibition of the swarming motility of *P. aeruginosa*. Reduction of pyocyanin production and LasA protease activity of *P. aeruginosa*.	[143]
Amphypterygium adstringens (Anacardiaceae)	Hexane extract	ND	*Chromobacterium violaceum* and *Pseudomonas aeruginosa*	Inhibition of the violacein production in *C. violaceum*. Inhibition of pyocyanin, rhamnolipid and decrease the elastase activity in *P. aeruginosa* without affecting cell viability.	[144]
Cecropia pachystachya (Cecropiaceae)	Aqueous extract	C-glycosyl flavonoids	*Chromobacterium violaceum* and *Escherichia coli*	Inhibition of QS.	[145]

Table 2
Medicinal plants containing biological active substances having anti-quorum sensing effects.

Name	Plant species	References
Vanillin	*Vanilla planifolia*	[101,146]
Taxifolin	*Cedrus deodara*	[102]
Eriodictyol	*Eriodictyon californicum*	[102]
3-indolyacetonitrile	Cruciferous	[147]
Iberin	*Armoracia rusticana*	[104]
Erucin	*Brassica oleracea*	[105]
Ajoene	*Allium sativum*	[106]
Houttuynin	*Houttuynia cordata*	[107]
Naringin	*Citrus sinensis*	[88]
Naringenin	*Citrus sinensis*	[87,88]
Kaempferol	*Citrus sinensis*	[88]
Quercetin	*Citrus sinensis*	[88]
Rutin	*Citrus sinensis*	[88]
	Cecropia pachystachya	[145]
Hesperidin	*Citrus sinensis*	[88]
Apigenin	*Citrus sinensis*	[88]
Neohesperidin	*Citrus sinensis*	[88]
Neoeriocitrin	*Citrus sinensis*	[88]
Casbane diterpene	*Croton nepetaefolius*	[96]
Epigallocatechin	*Acacia karroo*	[97]
β-sitosterol	*Acacia karroo*	[96]
Ellagic acid	*Termanilia chebula*	[75]
Cinnamaldehyde	*Cinnamomum zeylanicum*	[82]
Sesquiterpene lactones	*Centratherum punctatum*	[83]
Sesquiterpene lactones	*Vernonia blumeoides*	[141]
Methyl eugenol	*Cuminum cyminum*	[84]
Curcumin	*Curcuma longa*	[85]
Zingerone	*Zingiber officinale*	[98,148]
Tannic acid	*Quercus infectoria*	[86]
Chlorogenic acid	*Cecropia pachystachya*	[145]
Isoorientin	*Cecropia pachystachya*	[145]
Sovitexin	*Cecropia pachystachya*	[145]
Isovitexin	*Cecropia pachystachya*	[145]
Vitexin	*Cecropia pachystachya*	[145]

complex chemical structure, and their presence was confirmed in medicinal plants products [87,99,100].

Compounds such as vanillin in *Vanilla planifolia* [101], naringenin in *Citrus sinensis* [87], taxifolin in *Cedrus deodara* [102], eriodictyol in *Eriodictyon californicum* [103], methyl eugenol in *Cuminum cyminum* [84], iberin in *Armoracia rusticana* [96], erucin in *Brassica oleracea* [105], ajoene in *Allium sativum* [106], houttuynin in *Houttuynia cordata* [107], as well as naringin, naringenin, kaempferol, quercetin, rutin, neoeriocitrin in *Citrus sinensis* [108] were reported to inhibit QS signaling pathways.

7.3. Plants as a source of anti-QS drugs: experimental studies and mechanisms of action

The use of medicinal plants as anti-QS needs some sophisticated experimental methods. This includes the screening of antibacterial medicinal plants based on several approaches such as ethnobotanical use and the ecological destruction and taxonomical classification of such medicinal plants. To reveal antibacterial effects, researches use disk diffusion or agar well diffusion assay to determine antibacterial inhibition. These are just indicative tests that confirm antibacterial effect. For further studies, it is necessary to determine the MIC using micro-broth dilution assay or just turbidity tests. For investigation of mechanisms of action, several methods have been used and at each step of evaluation, the bio-guided fractionally is intersecting for targeting the natural bioactive molecules from a medicinal plant. Some bacterial species such as *Chromobacterium violaceum* (*C. violaceum*) and *P. aeruginosa* are often used for studying the anti-QS activities of antibacterial agents such as natural substances. The anti-QS action of these molecules and others are implicated in the several mechanisms targeting numerous ways such as AHL synthesis, AHL receptors, AHL dissemination and biofilm formation. Figures 3 and 4 summarize the principal mechanisms of action that could inhibit QS.

7.3.1. Action of medicinal plant products against QS molecules

Essential oils produced by aromatic plants have been observed to be effective against biofilms formed by certain bacterial strains such as *Salmonella*, *Listeria*, *Pseudomonas*, *Staphylococcus* and *Lactobacillus* spp. [109,110]. The inhibition of bacterial QS can take place through various mechanisms (Figures 3 and 4), including (1) inhibition of AHL synthesis; (2) inhibition of transport and/or AHL secretion; (3) sequestration of AHL; (4) antagonistic action of HLA mediation; and (5) inhibition of targets downstream of the AHL receptor [72,111,112]. Some recent studies have targeted the anti-QS activity of essential oils and their major components [82,89–91,113,114]. Amongst the essential oils tested against the QS, we can cite those of lavender, clove and rosemary [113]. Recently, Luciardi *et al.* studied the anti-biofilm and anti-QS activity of *Citrus reticulata* essential oil using *P. aeruginosa* as a study model. The results showed an inhibitory effect of this essential oil against biofilms formation at a concentration of 0.1 mg/mL, a reduction in cell viability of biofilm (41%) and a decrease in the production of the AHL system (33%) [89]. The HE of *Thymus vulgare* and its major compounds (carvacrol and thymol) were also tested for their anti-biofilm and anti-QS effects against *Pseudomonas fluorescens* KM121. The authors revealed a significant reduction in AHL production, a decrease in biofilm formation and flagella motility suggesting that inhibition of AHL and flagella genes prevents the biofilm formation [91]. Some compounds isolated from essential oils (chemotypes) are also shown to be effective against QS. For example, cinnamaldehyde inhibited bioluminescence in *V. harveyi* BB170 and eugenol in *P. aeruginosa* and *C. violaceum via* inhibition of virulence factor production such as violacein, elastase, pyocyanin and biofilm [114].

The anti-QS activity of organic extracts of medicinal plants is also addressed by some studies [92,93,115,116]. Plant extracts can act as QS inhibitors because of the similarity of their chemical structure to those of QS signals and/or their ability to degrade signal receptors (LuxR/LasR) [72,107,117]. Indeed, GABA (γ-aminobutyric acid), which is produced by certain plants, acts to promote signal degradation by OHC8HSL HLA lactonase (ATTM) in *Agrobacterium tumefaciens*, thereby limiting the process of QS-dependent infection [69,118,119]. *Emblica officinalis*, due to the presence of pyrogallol and its analogs, exhibits antagonism against Al-2 [120]. *Medicago truncatula* modulating AhyR, CVIR and LuxR activities in different organisms [121] and QS in *P. aeruginosa* and *Sinorhizobium meliloti* [111]. *Curcuma longa*, by the production of curcumin, inhibits the expression of the virulence genes of *P. aeruginosa* PA01 [122]. Extracts of certain varieties of apples and apple derivatives have demonstrated anti-QS activity, most likely due to the presence of different polyphenols, such as

Table 3

Anti-quorum sensing mechanisms of some molecules isolated from medicinal plants.

Compounds	Organism tested	Effects	References
Casbane diterpene	*Streptococcus mutans*	Inhibit ion of biofilms formation.	[149]
Epigallocatechin	*Listeria monocytogenes*	Reduction in cell numbers and inhibition of biofilms formation.	[96]
β-sitosterol			
Epigallocatechin	*Burkholderia cepacia* and *Staphylococcus aureus*	Reduction of biofilms formation by interference with AHL production.	[75]
Ellagic acid	*Burkholderia cepacia*	Reduction of biofilms formation.	[75]
Cinnamaldehyde	*Pseudomonas aeruginosa*	Inhibition of biofilms formation.	[82]
Epigallocatechin	*Eikenella corrodens*	Reduction of biofilms formation by interference with AI-2 system production.	[97]
Sesquiterpene lactone	*Pseudomonas aeruginosa*	Inhibition of AHL production and elastase activity.	[83]
	Chromobacterium violaceum	Affect cell–cell communication *in silico* and an antagonist effect against CviR protein to its receptor LuxR.	[142]
Methyl eugenol	*Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Serratia marcescens*	Reduction of AHL-dependent. Production of violacein, bioluminescence and biofilm formation.	[84]
p-Coumaric acid	*Pseudomonas aeruginosa*, *Escherichia coli*, *Agrobacterium tumefaciens*, *Chromobacterium violaceum*, and *Pseudomonas putida*	Inhibition of biofilms formation, inhibition of expression of bacterial virulence factor and antagonized the activity of LuxR, AhyR, and TraR receptor.	[30,150,151]
Curcumin	*Escherichia coli*, *Pseudomonas aeruginosa* PAO1, *Proteus mirabilis*, and *Serratia marcescens*	Attenuation of QS dependent factors such as exopolysaccharide production, alginate production, swimming and swarming motility.	[85]
	Pseudomonas aeruginosa PAO1	Reduction of biofilms and pyoacin formation by modulation of some genes expression implicating in QS signaling pathways.	[122]
	Escherichia coli, *Pseudomonas aeruginosa* PAO1, *Proteus mirabilis* and *Serratia marcescens*	Interference of curcumin with QS systems signaling of tested strains. Inhibition of biofilms formation and distribution of the mature biofilms. Attenuation of the QS-dependent factors, such as exopolysaccharide production, alginate production, swimming and swarming motility of tested bacteria.	[152]
Zingerone	*Pseudomonas aeruginosa*	Reduction of swimming, swarming, and twitching motility. Inhibition of biofilms formation.	[98,148]
	Chromobacterium violaceum and *Pseudomonas aeruginosa*	Inhibition of pyocyanin and violacein production	[153]
Tannic acid	*Staphylococcus aureus*	Reduction of biofilms formation by the effect on bacterial cell surface hydrophobicity	[86]
Naringin	*Chromobacterium violaceum*	Inhibition of biofilms formation, swimming and swarming motility. Induction of some gene transcription such as yenR, flhDC and fliA.	[87]
Naringin	*Yersinia enterocolitica*	Diminution of biofilms formation by decrease of AHLs production.	[87]
Vanillin	*Aeromonas hydrophila*	Inhibition of AHLs production.	[101]
Taxifolin	*Pseudomonas aeruginosa* PAO1	Downregulation of QS genes expression and diminution of Pyoacin production.	[102]
Sinensetin	*Escherichia coli* O157:H7	Diminution of biofilms formation.	[88]
Malic acid	*Escherichia coli* O157:H7 and *Salmonella typhimurium*	Inhibition of QS signaling by inhibition of AI-2 activities.	[154]
Flavonoids	*Vibrio harveyi*	Interfere with QS signaling in the bacterial model *V. harveyi*. Disruption of QS mediated bioluminescence by interaction with elements downstream LuxO in the QS circuit of *V. harveyi*. Exhibition of a strong dose-dependent inhibition of biofilm formation.	[155]
Thymoquinone	*Staphylococcus aureus*	Diminution of biofilms formation.	[156]
Vanillin	*Aeromonas hydrophila*	Diminution of biofilms formation by interaction with AHL receptors.	[157]
Salicylic acid	*Agrobacterium tumefaciens*	Diminution of biofilms and AHL production by Modulation of 103 genes family involved in virulence.	[158]
Salicylic acid	*Pseudomonas aeruginosa*	Inhibition of several QS receptor production.	[159]

(*continued on next page*)

Table 3 (*continued*)

Compounds	Organism tested	Effects	References
Rosmarinic acid	*Pseudomonas aeruginosa* PAO1	Diminution of biofilms formation.	[160]
Resveratrol	*Proteus mirabilis*	Inhibition of QS mediators by inhibition of swarming motility and diminution of flagellin production.	[161]
Phenylacetic acid	*Pseudomonas aeruginosa*	Competitive action with AHLs signaling. Diminution of pyocyanin production of pyocyanin, EPS secretion, protease, elastase activities and swimming motility.	[162]
Malabaricone C	*Pseudomonas aeruginosa*	Diminution of pyocyanin and biofilms production by interference with QS systems	[163]
Farnesol	*Pseudomonas aeruginosa* PA14	Diminution of Pyocyanin and QS mediators level.	[164]
Dihydroxybergamottin and bergamottin	*Escherichia coli* O157:H7	Diminution of biofilms formation by inhibition of AI-1 and AI-2 activities.	[125]
Cinnamaldehyde and derivative compound	*Vibrio anguillarum*	Diminution formation of biofilms, pyocyanin, pigment and protease.	[84]

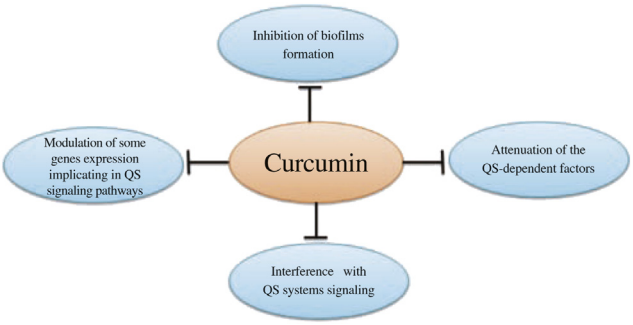

Figure 5. Quorum sensing molecular targets of curcumin.

hydroxycinnamic acids, rutin and epicatechin, which act as anti-QS agents in a synergistic manner against *C. violaceum* [123,124]. The Anti-QS effects have been showed by some other medicinal plants such as *Laurus nobilis*, *Rosmarinus officinalis* and *Pityriasis alba*. The effects of these plants were showed capable to decrease the violacein production [125]. The hydroalcoholic extracts of *Berberi saristata* and *Camellia sinensis* showed anti-adhesion and anti-biofilm activities indicating a stoppage in the production of the QS molecules in *E. coli*. On the other hand, the *in silico* analyses support the anti-QS action of the phytomolecules present in these extracts (flavonoids, alkaloids and tannins) *via* an antagonistic activity of LuxS [115]. The fractionation of the extracts still makes it possible to screen chemical families and sometimes molecules which could have important effects. Indeed, Vasavi *et al*. showed that the *C. asiatica* ethyl acetate fraction (very rich in flavonoids) decreased the production of pyocyanin and biofilms formation by inhibition of elastolitic and proteolytic activity in *C. violaceum* [93].

Other extracts, such as ethanol and ethyl acetate extracted from *Hypericum connatum*, have an anti-QS activity against *C. violaceum*, which limits its production of violacein [126]. Polyphenolic compounds with a gallic acid moiety, such as epigallocatechin gallate, ellagic acid and tannic acid, which are commonly produced by many medicinal plants, are capable of specifically interfering with the mediated signaling of AHL by blocking communication between bacteria within the same population [17,127]. For example, grenades and berries are rich in ellagitannins such as punicalagin and ellagic acid [128]. In the intestine, ellagitanins are hydrolysed to ellagic acid by the microbial flora and then metabolized to form urolithin-A and urolithin-B. These metabolites can then accumulate in the human intestine, where they have important functions. Indeed, urolithin A and B are also able to inhibit the processes associated with QS and decrease the levels of AHL produced by *Enterocolitica entheropathogen* [129]. Certainly, the anti-QS activity of natural substances depends on the bacterial strain tested, the extract tested or the molecule and the experimental method used. The specificity of this activity, for each bacterial strain, involves the active principle and the target molecules of the QS.

7.3.2. Anti-QS action of isolated molecules from medicinal plants

The bio-guided fractionally method is used for identifying natural molecules from medicinal ones with specific pharmacological action. Numerous secondary metabolite molecules from medicinal plants that possess anti-QS effects have been isolated using bio-guided fractionally approach. Indeed, some furanones specifically interfere with regulated AHL processes [130]. Their

action is related to the acceleration of the AHL receptor protein degradation [131]. These results are due to the phylogenetic link between medicinal plant secondary metabolites and QS signaling molecules. There is a molecular mimetic; plant secondary metabolites mimic bacterial AHL and furthermore affect QS relation in bacteria, associated with action [121]. The screening of anti-pathogenic molecules from medicinal plants that could inhibit QS regulation in these pathogenic bacteria and their virulence factor production may predict some other anti-infective agents [132,133].

The recent studies deciphered numerous molecules from medicinal plants which have promising anti-QS activities. The cinnamaldehyde (major compounds of several plant essential oils) and some of their derivatives can inhibit several activities related to the QS such as biofilm formation [82,100]. The limonoids such as isolimonic acid and ichangin (molecules contained in bigaradier seed extracts) inhibit the growth of *V. harveyi* at a very low concentration and these mechanisms are related to the inhibition of HAI- and AI-2-mediated bioluminescence [108]. Flavanones (abundant flavonoids in citrus) have been shown to be capable to interfere with QS detection and influence some other related physiological processes [87]. Flavonoids, such as naringenin, quercetin and apigenin, have been demonstrated as inhibitors of bioluminescence HAI-1 or Al-2-mediated production in *V. harveyi*. Some flavanones such as naringenin and taxifolin reduced the production of pyocyanin and elastase (QS related molecules) in *P. aeruginosa* without affecting bacterial growth. These two molecules also reduced the expression of several genes controlling QS in *P. aeruginosa* PAO1. Naringenin has also been shown to be able to considerably reduce the production of QS mediators such as N-(3-oxododecanoyl), lactone-1-homoserine (3-oxo-C12-HSL), acyl-homoserine lactone and N-butanoyl-1-homoserine lactone (C4-HSL) [86].

Other flavonoids such as quercetin, sinensetin, apigenin inhibit the formation of biofilms in *V. harveyi* BB120 and *E. coli* O157:H7 [87,88]. In *P. aeruginosa* PAO1, some flavonoids such as the catechin and flavanes-3-ol reduced the virulence factors (pyocyanin and elastase) induced by QS signals. The reduction of these factors inhibits the biofilm formation [134,135]. The HLA molecules have been degraded some legume products (alfalfa, clover, lotus, peas and yam beans) [136,137]. Also, directed action on biofilm formation has been reported grape fruit juice and rosmarinic acid produced by the roots of *Ocimum basilicum* against *E. coli* [56].

Curcumin, a compound isolated from *Curcuma longa,* has many targeting pathways against QS activity (Figure 5). This molecule can attenuate the QS dependent factors such as exopolysaccharide production of several pathogenic strains such as *E. coli*, *P. aeruginosa*, *Proteus mirabilis*, and *Serratia marcescens.* In addition, it has demonstrated that curcumin reduces some phenotypes related to the QS inhibition such as swimming, swarming, and motility. Some other characters such as the biofilms and pyoacin formation have been inhibited by curcumin in *P. aeruginosa.* The action was related to the modulation of several gene expressions implicated in QS signaling pathways.

8. Conclusion

With the development of bacterial resistance to antibiotics, the search for natural compounds extracted from medicinal plants that possess antibacterial properties is a necessary need. The deciphering of the QS system could offer other very effective anti-infectious routes of action, thus slowing the emergence of bacterial resistance to antibiotics. However, extensive research using colossal technologies is challenging in order to demonstrate natural molecules with selective pharmacokinetic bioavailability and specific pharmacodynamic actions against numerous QS and biofilm mediators to counteract bacterial resistance.

Conflict of interest statement

The authors declare that there is no conflict of interests regarding the publication of this article.

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