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Review Article

Natural Anti-Quorum Sensing agents against *Pseudomonas aeruginosa*

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Abstract:

Abuse of antibiotics in therapy has led to development of resistance in the target organisms. Failure of the current antibiotics to control infections makes it essential to discover alternative drugs. The pathogenicity in numerous bacteria is regulated by Quorum sensing (QS) signaling systems. The QS inhibition system may cause the reduction of virulence and defense against the bacterial infections. The QS is the main regulator of virulence and biofilm formation in *Pseudomonas aeruginosa*. A variety of plants showed their effects on *P. aeruginosa* virulence. Extract of various plants control the regulatory QS genes and factors with marginal effects on bacterial growth. The quorum-quenching (QQ) mechanisms are unrelated to static or cidal effects. In fact, anti-QS have already shown promise in the battle against *P. aeruginosa* infections.

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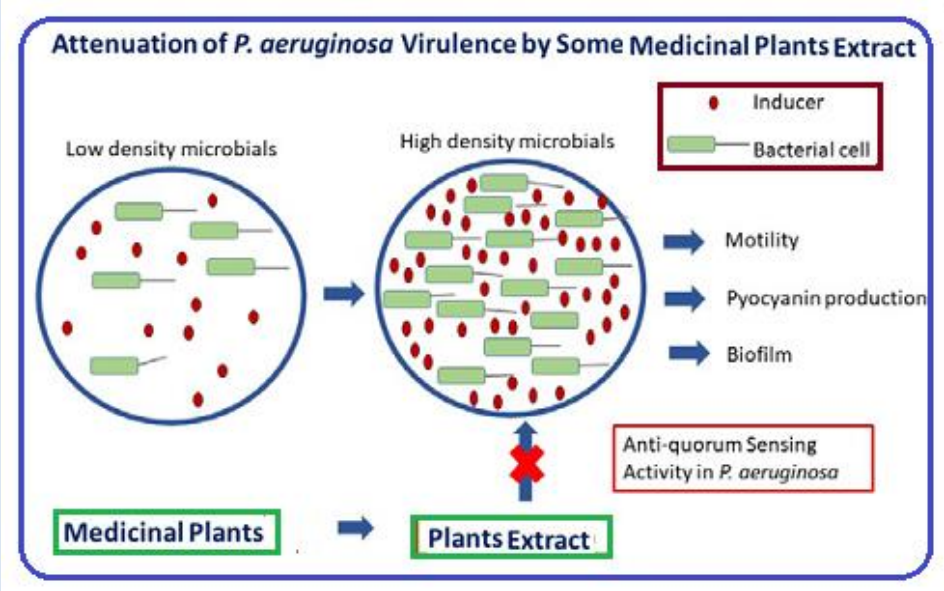
Graphical Abstract:



Biography:

Mohammad Asif was born in India. He studied **Bachelor of Pharmacy (**Pharmaceutical Chemistry) from IFTM, Moradabad, affiliated with Rohilkhand University Bareilly (U.P) in year **2003**. He received the M.S. degree in Pharmaceutical Chemistry at Bundelkhand University Jhansi (U.P) in **2006** and the Ph.D degree also in Pharmaceutical Chemistry at Uttarakhand Technical University, Dehradun in year **2015**. He focused his doctoral thesis on the Synthesis and biological evaluation of some new pyridazine-3(2H)-one derivatives. His research interests focus on the Medicinal Chemistry, Inorganic Chemistry, Organic Chemistry, Chemistry of Natural Products, Pharmaceutical Analysis and Physical Chemistry.

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1. Introduction

To defeat the difficulties of antibiotic therapy against the resistant infections, using the novel remedies is of a great importance. *Pseudomonas aeruginosa* is a notorious bacterium due to its substantial virulence factors, affinity to form stubborn biofilm and the most prevalent cause of the nosocomial infection such as Pneumonia and urinary tract (UT) infections. *P. aeruginosa* has revealed an increased resistance towards the antibiotics including imipenem, quinolones, and cephalosporins [1]. To struggle against these infections a broad study on the novel antimicrobials is required. The current approaches against these infections are quorum sensing (QS) inhibition. The QS is not only a population-dependent fact by which bacteria make sense about their population solidity but also is a controller of diverse roles such as luminescence, bioflim development, and virulence factor production. Disruption of the bacterial cell-cell contact is identified to attenuate virulence, while restrictive selective strain toward bacterial resistance. Plants can make diverse antimicrobial substances such as quinones, flavanones, phenolics, catechins, polyphenolics, alkaloids, and terpenoids. Like antibiotics, these substances are aiming at killing of the pathogens and work via a specific mechanism like disrupting microbe cell membranes. However, plants have a different way of dealing with microbes for targeting microbe cell's communication system. The intercellular communication in bacteria is identified as quorum sensing (QS). Anti-QS agents were first described in the red marine alga, *Delisea pulchra* [2] in a south Florida [3]. In this review, we discussed an ethnobotanically directed exploration for QS inhibiting agents in several medicinal plants for anti-QS action. The terrestrial plants not only generate autoinducer [6], a mimic to the bacterial QS system and respond to microbial signals [7, 8] and discussed about complications related to *P. aeruginosa* infection and the plants which could showed potentially novel therapeutic way for the treatment of *P. aeruginosa* infections. Recently, *Conocarpus erectus*, *Tetrazygia bicolor*, *Chamaesyce hypericifolia*, *Callistemon viminalis*, *Bucida buceras*, and *Quercus virginiana* revealed anti-QS effects using *Chromobacterium violaceum* and *Agrobacterium tumefaciens* NTL4 as biomonitors [9-12].

2. Quorum Sensing: a Novel Target

Quorum sensing (QS) is a population-dependent event [13]. The capability to sense the size of a bacterial population is arbitrated through small signaling molecules or autoinducers [14, 15]. These molecules are continually formed and received at a basal level by bacterial cells. There is an excess of signaling molecules in the surroundings, with high population density and the signals diffuse back into the cell where they ease the regulation of gene expression [14]. The QS systems are everywhere among bacteria, controlling the diverse functions such as biofilm formation, luminescence, antibiotic, virulence factor formation, pigment formation, plant-microbe interactions and motility [16, 17]. Although there are a various different QS systems [18], the most broadly studied prototype is based on the Lux system of *Vibrio fisheri* and *V. harvey*i [19, 20]. This QS event engages a three part system: a liberally diffusible signal, a synthetase to make this signal, and a regulator that interacts in union with the signal to control the gene expression.

The key signaling molecules formed by Gram-negative bacteria are acyl-homoserine lactones (AHLs) [21]. In *V. fisheri*, LuxI makes an AHL signaling molecule which is connected to LuxR at a certain level [20, 22]. This level is reached only when enough bacteria are present (a quorum) to create sufficient amounts of the AHL [23-26]. The AHLs connect to LuxR (product of *luxR*) at a certain level, activating transcription of *luxI* and the luciferase genes [18]. AHL-mediated QS systems based on the LuxI/R pattern have been distinguished in human pathogens like *P.aeruginosa* [27], *Yersinia pseudotuberculosis* and *Escherichia coli* [28], and plant linked bacteria like *Rhizobium leguminosarum* [29], *Erwinia carotovora and Ralstonia solanacearum* [30]. In every case, QS systems can control virulence. Thus, the innovation of QS has given us a novel target to attack and attenuate bacterial pathogenicity [31-34].

3. Mechanisms of QS Inhibition

There are numerous ways to inhibit cell-cell communication together with competitive inhibition, signal binding, signaling molecule degradation, and inhibition of upstream precursor or genetic regulation system [35]. These antagonists are based on the C12-AHL composition and cause a decline in LasR activity. AHL-antibodies developed to suppress QS during signal binding [36, 37]. A C12-AHL-protein conjugate was capable to reduce *lasB* expression, and a like molecule with greatly binding affinity for C12-AHL. Blocking the S-adenosyl methionine (SAM) or the fatty acid precursors essential to synthesize AHLs, reduced formation of the C12-AHL by LasI [38]. The genetic alteration of the upstream regulators such as Vfr and GacA has been shown to significantly reduce the QS action [39]. Various bacteria with *Bacillus* sp., *Arthrobacter* sp., *Variovorax paradoxus* and *A. tumefaciens* create lactonases, enzymes that cleave and neutralize the lactone ring of various AHLs [40, 41]. Lactonase expression in *P. aeruginosa*, outcome in a considerable reduces in AHL making and

virulence factor expression. The sensible use of anti-QS in drug resistant bacteria therapy is due to the increased occurrence of the drug failure by various pathogenic bacteria developing resistance to the presently used antibiotics [42, 43].

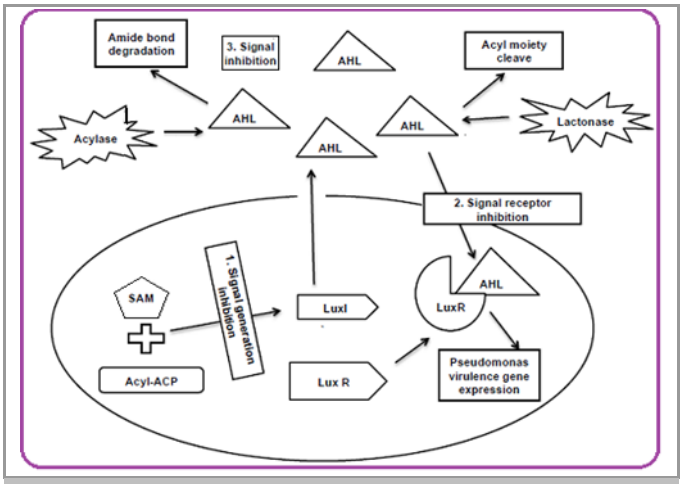

Figure 1. Three pathways of QS Inhibition in *P. aeruginosa* AHL mediated QS.

4. *Pseudomonas Aeruginosa*

Pseudomonas aeruginosa is an aerobic bacillus, Gram-negative, with length and width of 1.5-3.0 μm and 0.5-0.8 μm, respectively. It is motile, single polar flagella, oxidase-positive, non-fermentative and non-sporulating species [44]. Other diagnostic features are beta-hemolysis of blood agar, pigment formation together with pyocyanin (blue-green), pyorubin (red-brown), pyoverdin (yellow-green), and the distinctive grape-like odor. It is a ubiquitous organism with the capability to colonize varied role due to its range of metabolic and resistance abilities to the ecological faces [45].

5. Virulence Factors and Toxins

he pathogenicity of *P. aeruginosa* is a massive amount of secreted toxins and virulence factors such as rhamnolipid, superoxide dismutase, HCN, exotoxin A, phospholipase C, exoenzyme, pyoverdin, pyocyanin, LasA protease, and LasB elastase. Some of these factors may result in tissue necrosis and cell death. Pyoverdin, a yellow-green florescent pigment formed by *P. aeruginosa* to compete with mammalian transferrin for iron, the misuse of which really starves the host tissues [46]. It also encourages pathogenicity by exciting the bacterial growth [47]. LasA and LasB are zinc metallo-endopeptidases, belonging to the proteases family β-lytic endopeptidase enzyme. LasA has partial substrate specificity compared with the LasB; however, they play a key role in tissue plasticity in terms of elastin degradation. LasA cut elastin permitted it to be cleaved by LasB and other proteases. These proteases are capable of inactivating a extensive range of tissues and immunological agents [48, 49].

6. *Pseudomonas Aeruginosa* Disease Association

Due to the affinity to form obstinate biofilms, *P. aeruginosa* is not one of the microbes implicated in nosocomial infections. The *P. aeruginosa* is the second most ordinary cause of nosocomial pneumonia (17% of isolated microbes), the third most frequent cause of urinary tract infections (11%), fourth in bacterial species dependable for nosocomial infections (9%), the fifth most frequent cause of surgical site infections (8 %), and sixth most frequent isolated blood stream pathogens (3%) [1]. *P. aeruginosa* has only augmented in occurrence and antibiotic resistance, creating an exact threat for the vulnerable patients. *P. aeruginosa* has the capability to colonize various diverse infection sites when the host immune system is compromised. This can happen in patients with a severe basic condition such as AIDs, cancer, burn wounds, immune suppression from surgery, and organ transplant [50, 51]. Neonates are also very vulnerable to *P. aeruginosa* infection due to their immature immune system [52]. *P. aeruginosa* enter the body by any orifice and minor infections that may progress into severe and critical infections. In the ophthalmological system, *P. aeruginosa* can colonize and infect the cornea, aqueous humors and vitreous humors, or nearby structures after cataract or curative surgery. *P. aeruginosa* has been linked with a rising number of cases in contact lens-related keritis [53]. Infections can growth rapidly from minor conjunctivitis or keritis to scleral wounds and corneal ulcers due to cell lysis by *P. aeruginosa* extracellular enzymes. *P. aeruginosa* may also colonize in the auditory canal and cause minor otitis externa to inner ear problems (otitis media) [54]. Lacking proper handling secondary infections of the nearby bones (mastoiditis) or neurological structures can happen [55-58].

Distraction of the gastrointestinal (G.I) system often happens in pediatric patients or those with neutropenia or blood linked disorders [59]. Colonization in the gastro-intestine can range from diarrhea to severe rectal wounds and necrotizing enterocolitis in patients. Urinary tract infections (UTIs) are general due to regular catheterization and the existence of drug resistant bacteria [60]. If left unrestricted, these infections can lead to kidney disorders and renal failure. Proximal bone infections like osteomylitis of the lumbosacral vertebrae and pelvis can happen as a secondary hurdle to UTIs [61]. The *P. aeruginosa* infection can also happen by an scrape or break in the skin, due to wound, surgery, catheterization and dermatological conditions like dermatitis or folliculitis [62] to life threatening cases of cellulitis or

necrotizing fascitis. Infections with deep tissue injure particularly in burning state can extend to the bloodstream, causing bacteremia and septicemia [44]. Blood borne *P. aeruginosa* can go to heart, causing endo-and pericarditis. Complications in the pulmonary system can start as sinusitis or an upper respiratory tract infection and lead to pneumonia, bronchitis, or pulmonary lesions. Infections of the sinuses can also cause meningitis and cerebral lesions due to the nearness to the brain.

7. Current Treatment Procedures

The current treatment procedures can vary greatly since a patient may be infected with one or more drug resistant *P. aeruginosa* strains. Therapeutic tactics to treat infections are including the use of a single antibiotic or combination of two or three antibiotics drugs. Monotherapy has normally dealing with β-lactam antibiotics such as penicillins, cephalosporins, or newer β-lactams like imipenem and meropenem. These antibiotics act by interfere with the production of peptidoglycan into bacterial cell walls. Unfortunately, *P. aeruginosa* has evolved an efficient way of inactivating these drugs, leading to a novel approach for the treatment [63].

Anti-pseudomonal mixtures are including a combination of a β-lactam like aztreonam, ticarcillin or ceftazidime plus a β-lactamase inhibitor like sulbactam, and aminoglycoside antibiotic like tobramycin or amikacin. Aminoglycosides are interfering with protein production by binding to the 30S ribosomal subunit of the bacterial cells. Combinations of ceftazidime and fluoroquinolone like ciprofloxacins are also effective. The quinolones are exhibiting their bactericidal action by blocking DNA replication through inhibition of gyrase [64]. Option combinations include pairing ciprofloxacin with animoglycoside or with the broad-spectrum antibiotic fosfomycin, which prevent cell wall formation by inhibiting production of N-acetylmuramic acid [65]. However, there are a few achievements in eliminating *P. aeruginosa* with these treatments, many patients need continuing treatment and toxicity can extend with the recurrent use. There is an increased trend of antibiotic resistance that will quickly provide this therapeutics uselessness.

8. Antibiotic Resistance in *Pseudomonas Aeruginosa*

A21.1% of the nosocomial infections were imipenem resistant which enhanced 15% over the last five years (1998-2002). Similarly, 29.5% of *P. aeruginosa* infections were resistant to quinolones and 31.9% were resistant to cephalosporins, which enhanced 9% and 20% over the previous five years, respectively [1]. The encouragement of antibiotic resistance occurred, either through overuse and successive mutation or via gene transfers. The more recently acquired resistance mechanisms *P. aeruginosa* has several factors that are measured intrinsic. The pathogenic strains of *P. aeruginosa* possess creative mechanisms which reduced antibiotics vulnerability including:

A. Biofilm development

B. Restricted surface accessibility

C. Exclusion via efflux pumps

D. Enzymatic inactivation of antibiotics

E. Modification of target proteins

A. Biofilm formation

The planktonic method for bacterial growth has been widely studied, and it was found that most of the bacteria survive in nature as component of a surface-adherent, matrix-enclosed biofilm [11]. *P. aeruginosa* is not an exception to this rule, and some strain of it can control a mucoid phenotype through infections [63]. Due to the secretion of an exopolysaccharide, biofilm cells form a slime layer in which they are permanently bound to a substratum and to each other [66]. This protected pattern results in changing the growth rates, transcription patterns, , an improved ecological resistance from that of their planktonic counter parts [67]. Antimicrobials are prohibited from getting the innermost cells of a biofilm and are therefore incapable to completely eliminate the infection [68]. The alginate layer of mucoid *P. aeruginosa* avoids optimal host immune role by masking antibody opsonization and inhibiting clearance [69]. The latter is accomplished by promoting permanent adherence of the bacteria to lung epithelial cells [70-72].

9. *Pseudomonas aeruginosa* QS specifics

Complexity in treating obstinate infections and the growing resistance to antibiotics, new remedial tactics are becoming more necessary. Targeting the QS system of *P. aeruginosa*, one of the main complicated pathogens in the lung, is an original plan of attack. This arrangement is a key controller of pathogenicity in *P. aeruginosa* and other relevant bacteria, thus inhibition of QS may decrease the virulence and defend against infections [73, 74]. The QS system of *P. aeruginosa* is based on the *luxI-luxR* prototype. This complicated QS communication system is reflected in various gram-negative bacteria, where it manages regulation of virulence with biofilm creation, motility, and toxin creation [75]. *P. aeruginosa* complicated two main sets of QS systems: *lasI-lasR* and *rhlI-rhlR* [41]. The LuxI homologues, LasI and RhlI, are synthetases that produce the autoinducer signaling molecules N-butanoyl-L-homoserine lactone

(BHL), and N-(3-oxododecanoyl)-L-homoserine lactone (OdDHL) respectively [76]. These signaling molecules diffuse out into the environment, reaching a supposed threshold meditation that may activate the receptors *lasR* and *rhlR* [77]. These receptors coordinate directive of pathogenicity through transcriptional activation of various virulence factors [78, 79]. A third signal, PQS (*Pseudomonas* Quinolone Signal) plays an essential role in the QS system and is concerned in the creation of *N*-(3-oxohexanoyl)-L-homoserine lactone (OHHL) [75, 77]. This secondary metabolite of *P. aeruginosa* is included into the QS hierarchy in times of cell stress, and interfering with this signal has been shown reduce virulence factor phrase [80] and a fourth system exists regulated by cyclic dipeptides (DKPs) [81]. This study focuses on the *las* and *rhl* systems [82]. The superfluous and auto-regulatory nature of the QS system is fairly complex [83], the *P. aeruginosa* QS hierarchy suggests that *las* controls *rhl* with virulence proteins [41]. The virulence factors LasA (staphylolytic protease) and LasB (elastase) are under control of the *lasI/R* system [84], however *rhlI/R* also controls effect to a lesser amount [85]. Pyoverdin is under *rhlI/R* control [85], whereas biofilm formation is partially under QS control [67]. The *las*-*rhl* system also falls under the umbrella of various "global" regulators like Vfr (homologue of *E. coli* cAMP receptor protein, CRP) [39] or GacA (sRNA binding protein) [78]. Control from these genes also influence downstream virulence and thus to inhibit pathogenicity and a therapeutic agent could display an effect directly on the *las*/*rhl* system or the PQS or DKP pathways. The halogenated furanones inhibit *P. aeruginosa* both *in vitro* and in a murine models [86, 87]. These compounds act by transferring the signaling molecule from its receptor, thus accelerate receptor turnover [88, 89]. They also have persuaded on siderophore biosynthesis [90].

10. Ethnobotany and Ethnopharmacognosy: Looking to the past for explanation of the future

The excess use of antibiotics began a rising tendency of resistance in various pathogens. Even though combinatorial and synthetic chemistry can offer us with some clarification for infectious diseases, various medicinal compounds already present in nature and are pending to detection [91-93]. The high biological range is a possible linked to high chemical multiplicity, allow for the development of many toxic and bioactive plant substances. Plants create precise compounds to provide desires like reproduction and defense [3, 9, 76]. Plants have evolved toxic and bioactive substances to defend against herbivores and pathogen attacks [94] because plants have relied more heavily on chemical defenses than motile organisms. In lots of cases, the connection between toxin and medicine is dosage, and numerous plant toxins have originate their way into pharmacopoeia, example, foxglove or *Digitalis spp.*, if ingested, can generate convulsions, bradycardia, cerebral disturbances and eventual death [95]. Though, at the correct dosage, the cardiac glycosides digoxin and digitoxin have effective in the treatment of atrial fibrillation and heart failure [96].

11. Advantages of a directed search

Large numbers of plants with chemical variety are the basis for testing medicinal compounds [97]. Though, unite these natural qualities of plants make even better place in search for new drugs. Most plants have some type of constitutive or inducible resistance against pathogens, but plants used medicinally may also have chemical defenses to human pathogens [98].

12. Relating traditional and modern medicines

Expressive the traditional use of the plants can guides drug discovery and giving an idea of its potential use in the society. For example, plants used as snakebite medication may be useful in discovery hypotensive drugs. If an individual wants to survive the bite of a snake, it is beneficial to lower the blood pressure and slow the heart rate so as to not reach the venom or poison to susceptible organs before it could be metabolized. This led to the finding of hypotensive alkaloids in Rauwolfia (Apocynaceae) spp., [99]. Ethnopharmacology is beneficial to traditional medicinal societies and support to modern scientific methods to help and improve healthcare in rural areas. The ethno-pharmacology study would begin with the cultural anthropology of a group and their medical system in the context of culture and include local medical data to avoid loss of information to upcoming generation. The botanical, chemical, and pharmacological studied of the plants give potentially useful and unique medicinal drugs. Each of these parts (botany, anthropology, pharmacology and chemistry) could take time to fully explore. Thus, most studies focused on aspect of ethnopharmacology depending on the expertise and interests of the investigators.

13. Botanicals as anti-bacterial therapies

Various ethno-botanical explored for antibacterials, confirmed not only the requirement for drugs but also the numerous plant species that utilized for bacterial circumstances [100]. While medicinal plant researches have led to the discovery of various key drugs like morphine, quinine, camptothecin and paclitaxel, there is not a huge degree of overlap between generally used plant drugs and antimicrobials [101-105].

14. Tea tree oil

Melaleuca alternifolia Cheel (Myrtaceae)/tea tree is an aromatic tree. The essential oil of *M. alternifolia* is a topical antimicrobial, its activity has attributed to terpinen-4-ol, a main mono-terpenoid of the oil [10]. Other terpene constituents include γ-terpinene, α-terpineol, cineole and *p*-cymene [99]. Monoterpenoids are present mainly in plants with volatile oils like those in the Lamiaceae, Myrtaceae, and Rutaceae. These compounds causes membrane disruption in bacteria (Cowan 1999).

15. Oregano oil

Origanum vulgare L. (Lamiaceae) is a herb, essential oil fraction is effective against bacterial and fungal infections in gastrointestinal and genitourinary tract [106,107]. Its antimicrobial activity is recognized to the phenolic monoterpenoids, carvacrol and thymol, along with various other terpene alcohols, phenols and sesquiterpenes [108]. The two main chemotypes of *O. vulgare* showed either high thymol or high carvacrol substance [108], both are antimicrobial [100], though the latter is more effective [109]. The antimicrobial effect is due to membrane disruption [109] Oil of oregano has shows antibacterial effect against *Helicobacter pylori*, a causative agent of gastric ulcers [107], and a various clinically isolated pathogens including *Haemophyllus influenzae, Staphylococcus aureus, E. coli, Streptococcus pneumoniae,* and *Enterobacter cloacae* [110] and also effect *in vitro* against *C. albicans*.

16. Myrrh

Myrrh is a oleo-gum resin of *Commiphora* Jacq. species of Buseraceae family. It contained mainly aromatic peeling bark. *Commiphora* bark is achieved to collect the resin and has religious and medicinal use [100,106]. It is usually used in mouthwashes and toothpastes due to its antimicrobial effects. Myrrh consists of about 30-60% water soluble gum, 20-40% alcohol soluble resin and 8% volatile oils. The volatile oils fraction contains antimicrobial mono-terpenes like α-camphorine, myrcene and also furanosesesquiterpenes. The antibacterial effects of *Commiphora mulkul* (*Commiphora wightii* (Arn.) Bhandari) was showed *in vitro* antibacterial effect against various Gram positive and Gram negative bacteria [111]. It is also used for topically on wounds and oral and pharyngeal mucosa as a mouthwash [106].

17. Unused potential of plants for antimicrobial action

Plants are the main source of antimicrobial agents. In fact, about 75% of the antibiotics are derived from the actinomycetes (group of Gram-positive bacteria) [112]. Antibiotic-creating microbes possess genes which defend them from the toxic property of these compounds. It is easy for microbe to acquire antibiotic resistance through plasmid transfer or transposons. Plants are genetically dissimilar from the organisms they are trying to eradicate. There is small chance for a microbe to gain resistance from a plant. Plants produce a multitude of diverse antimicrobials like phenolics, flavanones, catechins, quinones, alkaloids, polyphenolics, and terpenoids [100]. Like antibiotics, these agents are targeted at killing the pathogen and work via a non-species specific means like disrupting microbial cell membranes. Plants have other way of deal with microbes-targeting cell's communication system or QS [12]. Breakdown of this system causes an attenuation of microbial pathogenicity [87]. The discovery of anti-QS agents in plants provides us with yet another type of antimicrobial agents.

18. Anti-Quorum Sensing from Ethnobotanicals

TDiscovery of compounds that inhibit QS, could provide a novel method of combating infection [42]. Anti-QS agents were first depicted in the red marine alga *Delisea pulchura*. This alga has anti-fouling property and contains halogenated furanones which block AHLs via competitive inhibition and destabilization of LuxR. The structural similarity allows furanones to inhibit the effect of AHL signaling molecules [89]. The QS inhibition defends themselves against the other microbes. Plant, bacteria, and fungi could produce compound which interfere the QS-regulated gene expression in pathogenic microbes [113, 114]. The discovery of AHL inhibitors in *D. pulchura*, anti-QS activity has found *Caulerpa* species and various higher plants including fruits and vegetables [115-117]. *Pisum sativum* (pea) seedlings and root exudates formed an inhibition of pigment production, exochitinase effects and protease activity in *C. violaceum* [116]. Carrot (*Daucus carota*), chamomile (*Matricaria* sp.), garlic (*Allium sativum*), water lily (*Nymphaea* sp.) and various peppers (*Capsicum* spp.) were possessing anti-QS activity against a *luxI*-gfp reporter strain. Toluene extracts of garlic exhibited anti-QS activity against Gram-negative transcriptional regulators Lux R or Las R [114]. Garlic can also inhibit biofilm formation in *P. aeruginosa*, and prevent nematode death [115]. Garlic and several plants such as *Thymus vulgaris* may intensify the killing effect against the Pseudomonas species [117,118]. Rosmarinic acid excreted from the root of sweet basil, is a caffeic acid ester with an inhibitory action on *Pseudomonas* species which may interfere with QS activity and bioflim formation [119]. Various fruits and herbs were found to have anti-QS activity in a *C. violaceum* strain and on the swarming motility of *E. coli* and *P. aeruginosa* [117].

Blueberry, raspberry, blackberry, cranberry, grape, ginger, oregano, kale, and turmeric exhibited moderate anti-QS actionv. Other than signal mimics like furanones, ellagic acid, tannic acid, and epigallocatechin gallate have shown anti-QS *action* in both an *E. coli* and *P. aeruginosa* strain [120]. The polyphenolics should be explored as anti-QS compounds. The antipathogenic anti-QS effects were exhibited with *Laurus nobilis* leaves, fruits, flowers, and bark extracts. The *S. oleraceus* exhibited prominent anti-QS activity, almost equals to *L. nobilis* extracts. *Rosmarinus officinalis* and *Tecoma capensis* leaves revealed moderate anti-QS activity. Weak anti-QS effects were observed with extracts of *Populus alba* (leaves), *Jasminum sambac* (flowers and leaves) and *Populus nigra*. Day by day anti-QS effects of several extract of natural plants extracts have been reported. Hexane extract of clove bud (*Syzygium aromaticum)* has significant anti-QS influence on the *P. aeruginosa* strains [121,122]. *Capparis spinosa* traditionally used in Italy, posses' antibacterial activity [123], methanolic extract of fruit of *C. spinosa* showed anti-QS activity on *P. aeruginosa* PAO1 strain [124]. Methanolic extract of the *Myristica cinnamomea* bark also have anti-QS action [125]. *Lagerstroemia speciosa*, known as 'jarul' prevalent in south-east Asia, revealed that this plant can modulate the QS of micro-organism specially *P. aeruginosa. Lagerstroemia speciosa* can attenuate QS-related genes (*las* and*rhl*) and their particular signalling molecules such as *N*-acylhomoserine lactones, but interestingly not affecting their growth by using a specific strain *P. aeruginosa* PAO1. Extract of *Melicope lunu-ankenda* edible plant of Malasyia, showed proficient anti-QS against P. aeruginosa PAO1. Some Chinese traditional system of medicine such as Cnidium monnieri, Angelica sinensis, Astragalus membranaceus, Aloe barbadensis, Lilium brownii, Crataegus cuneata, Dioscorea nipponica, Magnolia officinalis, and Ephedra revealed some activity against the pathogenic microbes including, C. violaceum and P. aeruginosa [127-130].

19. Conclusions

The plants have been used as a source of different types of medicinal compounds. Many ethnobotanically searches showed that these natural agents can be used as anti-pathogenic agents, mainly focused on antibacterial effects. Our focus on to anti-QS and anti-virulence property that may reveal quorum-quenching (QQ) compounds from plants for provide a novel method for the treatment of infections against resistant microbial strains particularly against *P. aeruginosa*. The actions of the plant extracts on *P. aeruginosa* are very complicated and perhaps beyond the area of the QS control hypothesis. The failure of accessible antibiotics to control the infectious makes it critical to find options to presently used drugs. The pathogenicity in numerous bacteria is regulated by QS that is the key regulator of virulence and biofilm construction in *P. aeruginosa* and other bacteria. Various plants extracts were showed effects on *P. aeruginosa* virulence factors and the QS has significant inhibition of LasA protease, LasB elastase, pyoverdin, and biofilm formation. In fact, anti-QS approach has shown promise in combat against the *P. aeruginosa* infections. However, the decrease of QS gene expression and signaling molecule levels and effect on virulence factor formation offer these plants were used in the future to combat *P. aeruginosa* and other bacterial infections.

Disclosure statement

No potential conflict of interest was reported by the author.

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