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Quorum sensing inhibitors: a tool for resistance against biofilm

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Abstract

Resistance among disease causing microorganism has increased, which inspire researchers to discover new antimicrobial drugs. In the field of medicine many researches have been conducted to find novel structures for the manufacturing of antimicrobial agents. Various biologically active compounds from plant have antimicrobial properties. Their ability is due to their anti-virulence characteristics. Quorum sensing is cell talking or communication mechanism in microbes which is based on microbial cell density and direct the virulence of many microbes by expressing certain genes. Quorum sensing has become an interesting goal for the manufacturing of new anti-virulent agents that do not depend on usage of antibiotics. Compounds which inhibit quorum sensing have the power to control development of disease. Medicinal plants, give us range of biological active compounds which control the disease process. These compounds are recently being studied to be an effective Quorum sensing inhibitors. So, the purpose of this review is to give a brief description of articles on plant and natural compounds with quorum sensing inhibitory effects.

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Introduction

Infections caused by bacteria, viruses, fungi and parasites are important cause of death and morbidity in all parts of world, especially in developing countries (Mohamed *et al.*,2014).Bacteria and fungi are becoming resistant to drugs in the last decade but the invention of new drugs has been decreasing continuously (Livermore, 2011). Disease occurring due to resistant microorganism can be dealt with combination of antibiotic with different mode of actions. The wide spread presence of pathogen resistance and the making of biofilm which is difficult to eliminate, have focus the efforts to find substitutes against present antimicrobial therapies which are not sufficient to eliminate the infectious microorganism. Thus studies are being performed to find noval therapeutic agents which are effective against these antibiotic resistant pathogens (Neuman *et al.*, 2013). A noval strategy is to target microbe's cell to cell communication which is known as quorum sensing (QS) it is the way by which microbes sense information from other cells (Chong *et al.*,2011).

The Quorum sensing mechanism based on the formation, dissemination and reuptake of autoinducer (AIs) in the surrounding medium the amount of which is depended upon the number of bacteria which secrete autoinducers. Autoinducers are substances which are collected outside the cell as signal molecule with respect to bacterial density are used as signals for communication inside the bacterial cell (Deep *et al.*, 2011). These signal molecule control gene expression in other bacterial cells of community which in turnmanages many bacterial activities. These activities include virulence, motility, luminescence, biofilm formation, sporulation, genetic competence and formation of antibiotics (Rocha *et al.*, 2010).Most important sequences for the species identification determined by identification of molecular markers (Ahmad *et al.*, 2019). Certain plants exhibit properties of plantbased medicines that contained chemical agents for the treatment of diseases (Ahsan *et al.*, 2019). Nutraceuticals used in the field of medicines comprised of vitamins used pharmaceutical industries (Ghani *et al.,* 2019).

Quorum Sensing are exhibited in the orange round when inhibitors of quorum sensing acting against AHL (Auto-inducers-2-based) Quorum sensing (Tang and Zhang, 2014). Some of the antibiotics in which azithromycin might be used as quorum sensing inhibitors at mild inhibitory concentrations (Swatton *et al.*, 2016). In quorum quencher peptide the purplish circle determines the Gram (positive) quorum sensing (Singh *et al.*, 2016). In scavenging auto-inducers as cyclodextrins or derivatives that represents bluish molecules (Morohoshi *et al.*, 2013) and antibodies AIP (AP4-24H11) and AHL (Fab RS2-1G9). Then green circles represents quorum quenching enzymes that disturb the quinolone PQS (HOD), AI-2 signals (QQ-2) and AHLs (Park *et al.*, 2007).

The different autoinducers are formed in Gram –ve and Gram +ve bacteria. These autoinducer and their receptors are divided into three major classes.N-acyl homoserine lactone (AHLs) are formed by gram –ve bacteria to manage various activities of bacteria through QS control of gene expression. The AIs are formed by LuxIproteins. Oligopeptides consist of 5 to 34 amino acids which act as autoinducer in Gram +ve bacteria. These peptides are transported by committed systems, posttranslational modified in many aspects and lastly recognized by other bacteria through receptors in their cell membrane.Autoinducer-2 hires by Gram –ve and Gram +ve bacteria for talking between species. The autoinducer-2 is chemically defined as furanosylboratediester formed by LuxS protein (Xavier and Bassler, 2003).

Selenium is a toxic metal that affect the living cells and causes growth of cancer cells (Shafiq*et al.*, 2019). In Gram +ve bacteria, Autoinducer are transferred out of cell by an ATPase exporter complex. When amount of Autoinducer got the threshold value, the protein kinase will be stimulated and will phosphorylate the response protein which will than bind to desired promoter which control QS gene(Finch*et al.,* 1998). Whereas in Gram –ve bacteria Autoinducer are synthesize and freely

releaseextracellularly. When autoinducer concentration get to a certain value it will induce its own synthesis, which increases concentration ofautoinducer. Now this AIs will bind to its receptors in the cell to form AIs receptor complex which then attach to specific promoter region to manage the QS gene expression. The quantity of auto inducer increase with growing number of bacteria which when reach specific value it diffuse back into bacterial cell initiate transcription of certain genes responsible for virulence, antibiotic production, biofilm formation (Finch *et al.,* 1998). Change in the function of bacterial cell by acyl homoserine lactone generate an expression of QS gene (Whitehead, 2001). LuxI protein produce AHLs and LuxR stimulate or inhibit the transcription of special genes which induce virulence (Morohoshi *et al*., 2008).

Quorum sensing (QS)

Inhibition of qs pathway

As QS is involve in many disease conditions it is possible that blockers of QS could be used to manage chronic diseases. QS Inhibition can be done in various ways, which is as under. Blocking of Autoinducer synthesis. Blocking of receptor binding of Autoinducer Receptor Antagonism. Segregation of Autoinducer by using antibodies against them.DNA barcoding is important to determine sequences found in specific region of DNA (Naeem *et al*., 2019). Destruction of autoinducer by enzyme like lactonases. InhibitingAutoinducer formation and transfer.Use of antibodies that inhibit Autoinducerreceptors (Delamo *et al*., 2007).

The Interference with the communication network or microbial Quorum sensing results in the weakening of bacterial attack (Smith and Iglewshi, 2003). Various ways has been proposed to interfere with quorum sensing which will have broad array of uses in Quorum sensing bases illness cause by microbes (Ditu *et al*.2011).

This forced the scientist on inhibiting this route by the usage of Quorum sensing inhibitors. Destruction of quorum sensing signal is also called Quorum quenching (QQ). This can be achieved by many ways such as by the formation of antibodies to Autoinducer substance or enzymatic destruction of autinducer molecule or the chemicals that inhibit quorum sensing molecules.

These measures interfere with cell talking and check the disease causing microbes without inhibiting their development, in this way antibiotic remain susceptible against bacteria (Chan *et al*., 2011).

The perfect QSIs is characterized as chemically stable, and highly efficient small molecules which have high level of specificity for QS controllers without harmful effect on microbes or on the host. Therefore synthesis of oval, nontoxic quorum quenching compounds from both herbal and microbial source, is having lot of advantage in recent years. Plants produce various substances such as simple Phenolic, flavonoids, alkaloids and terpenoids (Dewick, 2003).

Certain medicines also lead to cancer which started the growth of cancer cells (Naeem *et al*., 2019).

There biological activities and remedial roles are seen with vastconcern in beating Quorum sensing bacteria. As there is increase demand for QS inhibitor substances to counteract microbial resistance to drugs, it is essential to study and classify another and safe options for handling infectious microbes. Herbal compounds have long been used as medicine to control infections. The study of herbal and synthetic compounds can open up the possibility of using these compounds as QQ. This review presents the recent work on plant and synthetic sources which use as Quorum Quenching compounds.

Compound as quorum sensing inhibitors

In this topic quorum sensing activity of different compounds have been presented which has long been uses as medicine. The compounds which are derived from plants are usually phenols or their derivatives. These compounds havemany benefits for the plant survival and as well as antibacterial qualities against pathogenic bacteria (Choo *et al.,* 2003).

Table 1. Quorum sensing inhibitory compounds.

Sources	Antagonist	Inhibition against	Refrences
Plant	Centellaasiatia	*Chromobacteriumviolaceum CVO 26*	Vasavi *et al.*,2016
Plant	1,5- dihydropyrrol-2-ones	*E. coli*	W.K.Goh *et al.*,2015
Plant	Curcumin	*Pseudomonas aeruginosa (PAO1)*	Bahari *et al.*, 2017
Synthetic compound	Fructanase (FruA)	*Streptococcus mutans*	Suzuki *et al.*,2017
Synthetic compound	Glucosamine	*E. coli*	Nripendra et.al.,2017
Plant	Garlic	*Pseudomonas aeruginosa*	McCarthy and Gara,2015
Synthetic compound	Pyridoxallacthydrazone	*Pseudomonas aeruginosa*	Heidari *et al.*,2017
Plant	Resveratrol Piceatanol Oxyresveratrol	*ChromobacteriumViolaceum*	Sheng *et al.*,2015
Plant	Grape seed extract	*E.coli*	Sheng et. al.,2016
Plant	Eudesmanolidesesquiterpene lactone	*ChromobacteriumViolaceum*	Aliyu et.al.,2016
Plant	Malvidin	*ChromobacteriumViolaceum*	Gopa et.al., 2015
Plant	carvacrol	*Pseudomonas aeruginosa*	Tapia rodriguez et.al.,2017
Plant	Naringin	*ChromobacteriumViolaceum*	Tapia Rodriguez
Plant	Citric Acid	*E.coli*	Amrutha et.al.,2017
Plant	Monoterpene	*Pseudomonas aeruginosa*	Luciardi *et al.*,2016
Plant	Fructose-Furoic acid ester	*E.coli*	Vinothkannan *et al.*,2018
Plant	V-06-18	*P.aeruginosa*	Lu *et al.*, 2018
Plant	Resvertrol	*P.aeruginosa*	Zhou *et al.*,2018

The compounds which are derived from plants are mostly phenolics, phenolic acid, quinines, saponins, Tanins, coumarins, terpenoid, and alkaloids (Sharifi-Rad*et al.*, 2017). All of these different compounds show different quorum sensing inhibition because of their structural differences.

Centellaasiatca

Quorum sensing inhibitor activity of traditional herb *Centellaasiatca*. The effect of ethyl acetate extract of herb on QS regulated violacein production in *Chromobacteriumviolaceum* and formation of biofilm were studied. The ethanol extract of *C.asiatica* have shown quorum sensing inhibition in *C. violaceum* at 400 µg/ml, entirely stop formation of violacein without affecting the growth. This extract also shown inhibition of biofilm formation in *Pseudomonas aeruginosa*. The quorum sensing inhibition potential of this herb *Centellaasiatica*can be further studied for the synthesis of medicines attacking bacteria involving QS (Vasavi *et al.* 2016).

1,5-dihydropyrrol-2-one:The synthesize of 36 analogues of 1,5-dihydropyrrol-2-ones in sufficient amount through lactamization of fimbrolide. All these compound were characterized by many spectrophotometric analysis and then their Quorum sensing inhibition (QSI) activity has been evaluated against *E. coli.* The derivative 17a has shown the most activity with an AIC_{40}Value of 1.95 pursued by 9cwith an AIC_{40} value of 1.95 which shows that these compound are potent inhibitors**.** Moreover the binding affinity of derivative with the LasR receptor were also studied. The results showed that H-bonding and hydrophobic forces due to amino acid residue in LasR receptor help in binding of compounds to receptor (W.K.Goh *et al.*, 2015).

Curcumin

The synergistic action of curcumin along with antibiotic azithromycin and gentamycin in *Pseudomanasaeruginosa* (PAO1) quorum sensing related virulence factor.

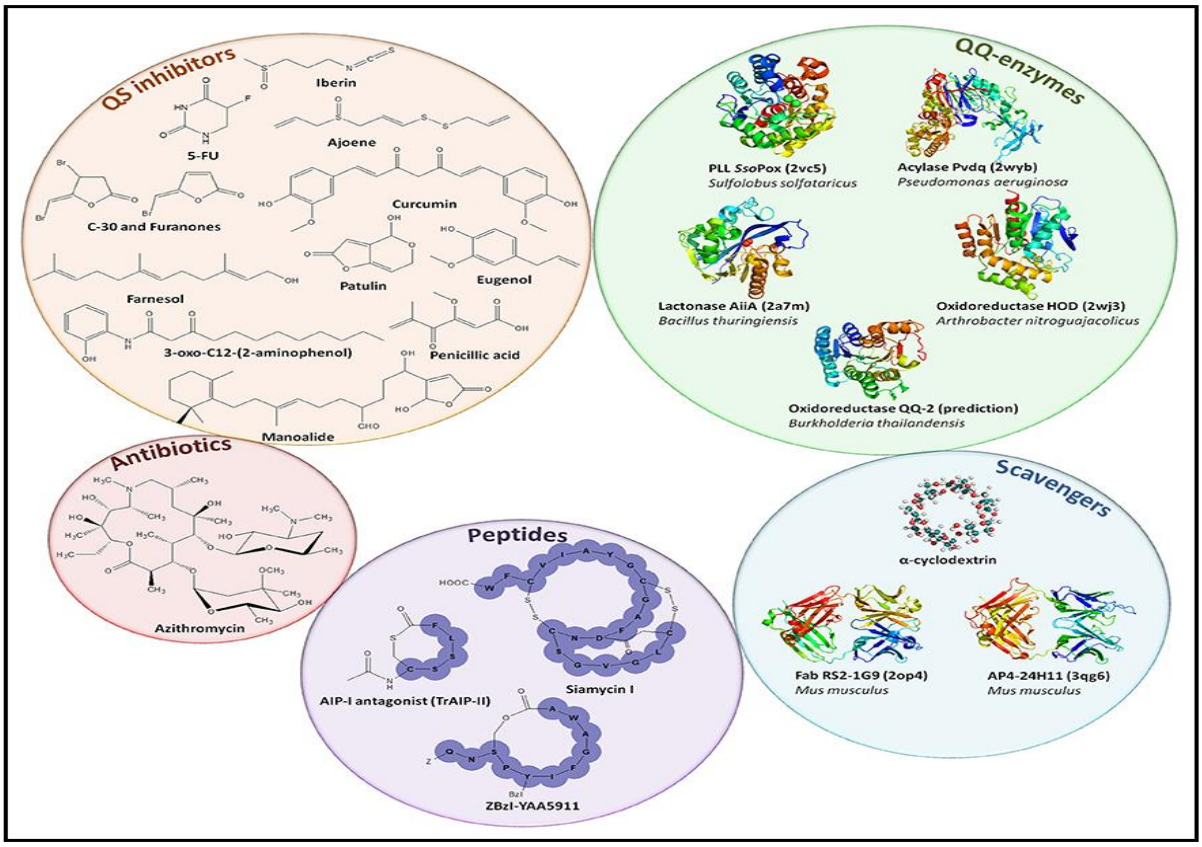

Fig. 1. Demonstration of quorum quenching agents.

Adding up of curcumin significantly lower the MICs of azithromycin and gentamycin. Curcumin had shown added affect with azithromycin and gentamycin. When bacterial cultures are treated with curcumin there is decrease in signal C12-HSL and C4-HSL. Expression of QS regulatory genes LasI, LasR, rhll and rhR using one by fourth of MICs of curcumin, azithromycin and gentamycin were decrease drastically compared to untreated *Psuedomonasaeruginosa*.Thus sub MICs of all these compounds have shown added effect when use together (Bahari *et al*, 2017).

Fructanase

*Streptococcus mutans*isbelonging to class of bacteria which cause tooth decay in human being. In this study inhibitory effect by Fructanase (FruA) on Competence stimulating peptide were projected as one of method for the blocking of glucan independent biofilm formation. The drop in sucrose concentration by Fructanase (FruA) leads to drop in glucan dependent biofilm formation and decrease of QS communication by FruA escort to decrease of glucan independent biofilm formation. Hence biofilm formation was decrease by the inhibition of both glucan dependent and independent biofilm formation (Suzuki *et al*., 2017).

Garlic**:** The activity of Garlic (*Allium sativum*) as quorum sensing inhibitor. Furthermore Garlic inhibit certain gene which are involve in quorum sensing in the Gram–vebacteriamost stubborn pathogen i.e*Pseudomonasaeruginosa*. Due to showing high level of quorum sensing activity of Garlic against *P.aeruginosa,* it is predicted that Garlic make this bacteria less pathogenic and more vulnerable to drug treatment (Ghani *et al*., 2019). The effectiveness of the drug tobramycin to kill Pseudomonas species *in vitro* improve significantly when given in combination with garlic extract (McCarthy and Gara, 2015).

Glucosamine

Glucosamine has been revealed to destroy the microbial quorum sensing system by blocking autoinducers.

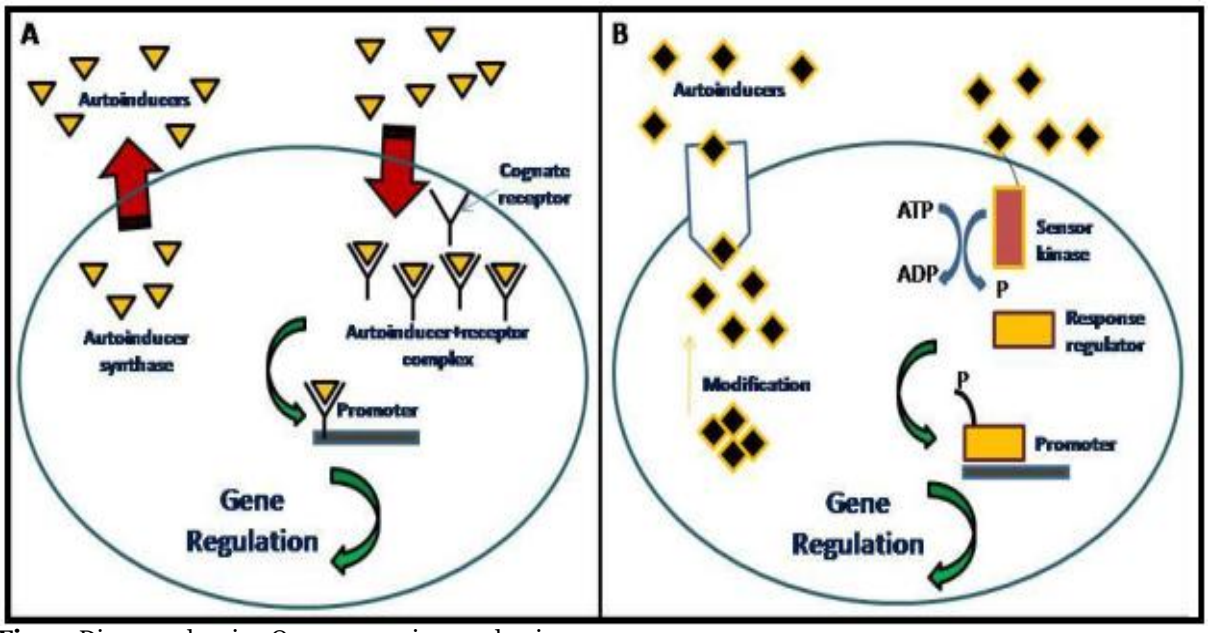

Fig. 2. Diagram showing Quorum sensing mechanism.

(A) Gram-negative bacteria: Signaling molecules are produce and diffuse out of the cell. When concentration of signal molecule reaches a particular level, a positive feedback will result in production of more signal molecule. Signal molecule will bind to its receptor to form signal molecule complex which then bind to specific promoter that lead to quorum sensing gene expression. (B) Gram-positive bacteria: A peptide signal molecule are modified and move out of the cell by ATP-binding cassette exporter complex. when concentration of peptide reaches a particular level it diffuse back into cell and induce sensor kinase protein which phosphorylate response regulator protein. This complex will bind to target promoter for regulation of QS gene expression.

In this article three glucosamine derivativeshas been derived by coupling method. The manufactured compounds were tested against 2 microbial strain i.e*Pseudomonasaeruginosa*and E.coli for quorum sensing activity. 9b compound have shown 79.1% QS inhibition againstP. *aeruginosa* and 98.4% against *E.coli* and compound 12b inhibited 64.5% against *P.aeruginosa*and inhibited 88.1% against E.coli. The capacity of compounds to block the formation of virulence factor pyocyanin and biofilm formation in *P.aeruginosa*was also studied (Biswas *et al*., 2017).

Pyridoxallacthydrazone

The action of pyridoxallacthydrazone against *P. aeruginosa*quorum sensing system. Study investigated the sub minimum inhibitory concof pyridoxallacthydrazone on virulence factors. *P. aeruginosa* culture which was treated by 1/4 and 1/16 MIC showed considerable blocking of virulence factors. Pyridoxallacthydrazone has also shown anti QS activity against *Chromobacteriumviolaceum*a Gram –ve bacteria. The docking studies also show that pyridoxallacthydrazone has the potential to block the lasR protein. The results point out that Sub MIC concentration of this compound display effect on *P.aeruginosa* quorum sensing related virulence factor (Heidari *et al.* 2017).

Grape seed extract

Evaluated the outcome of Grape seed extract on the growth, quorum sensing and virulence factors in *E.coli*. Toxin generating *E. coli* strains have becoming increasing distress to food industry. Al-2 is a global QS communicator used by a range of bacteria for communication and worldwide controller of virulence factor in *E.coli* (Sperandio *et al*., 2001)Grape seed extract inhibited AIs formation in six selected strains of *E.coli*in similar and dosage depended behavior.

Autoinducers 2 formation in 1-4mg/ml Grape seed extract treated groups was significantly reduced for all six strains tested (Sheng, *et al*., 2016).

Eudesmanolideses quiterpene

Antiquorum sensing ability of eudesmanolide Sesquiterpene lactone from plant *Vernoniablumeoides* was evaluated via quantification of quorum sensing controlled violaceinmanufacturing and qualitative modulation of QS activity and signal production by means of agar diffusion double ring test using three biosensor system. Based on biological research of the quorum sensing inhibitory ability of eudesmanolideses quiterpene lactone from *V. blumeoides*, it may be said that they have the ability to be new anti-pathogenic agent with the ability to lessen virulence and pathogenicity of medicine resistance bacteria in vivo (Aliyu, *et al.*, 2016).

Syzygiumcumini

The present study aimed to evaluate the QS blocking ability of *Syzygiumcumini* by using a strain of *Chromobacteriumviolaceum*. The extract of *S. cumini* in ethanol has been performed and was evaluated its antibiofilm activity against opportunistic pathogen and by performing docking analysis with LasR receptor protein. Synergistic activity of conventional antibiotic with Anthocyanin increases the susceptibility of *K. pneumonia* by 58%. Docking analysis conformed that the actual active compound in *Syzygiumcumini*ismalvidin. The malvidin has shown strong ligand bonding with lasR protein and also find out the effect of malvidin to reduce violacein production, biofilm formation, EPS production of *K.pneumoniae* in dose dependant manner. These finding suggest that *S.cumini* could be used as QS base antiquorum sensing and antibiofilm agent (Gopa, *et al.*, 2015).

Stilbenoid

The quorum sensing inhibitory effect of 10 stilbenoid and their potential structure activity relationship has been studied. Out of ten stilbenoids only three including resveratrol, piceatannol and oxyresveratrol had shown antiquorum sensing activity and it may be due to double bond in the stilbenoid structure. Furthermore the number and position of –OH group in stilbenoid also determine its QSI activity. More studies on it confirm that above mention compounds had outstanding QSI activity without disturbing growth of microbes. So the resveratrol, piceatannol and oxyresveratrolcould be used in manufacturing of new compounds controlling virulence (Sheng, *et al.*, 2015).

Carvacrol

Carvacrol as a QS inhibitor compound in Pseudomonas *aeruginosa*. MICs of carvacrol against free floating *P.aeruginosa*was 7.9mM. The smaller amount of carvacrol to study MICs were applied to view alterations in QS activity and biofilm formation of to evade effect of cell death. Carvacrol check biofilm formation of *P.aeruginosa* at conc of 0.9 to 7.9 mM contrast to non-treat bacteria.Pyocyanin formation by *P.aeruginosa* was lessen to about 60% at 3.4mM of carvacrol. Higher doses of carvacrol resulted in the death of bacteria. Whereas pyocyanin a toxin produce by bacteria reduced up to 50% at 0.7mM of carvacrol without causing any harm to pathogen. These results imply that carvacrol could be used to develop new and protected broad spectrum drugs and anti QS compounds (Tapia-Rodriguez *et al.*, 2017).

Pummel peel

The chemical composition, antimicrobial and anti-quorum sensing activities of pummel peel flavonoid extract. The flavonoid content of pummel peel was rutin and its primary constituent were naringin and acetyl naringin making about 91% and 4 % respectively. The MICs of flavonoid against the tested bactaria ranged from 0.5 to 4.5 mg rutin/mL. The sub inhibitory conc of flavonoid block the virulence effect cause by QS system operating in bacteria. Violacein formation in C. violacein was checked by 73% by adding 0.9mg Rutin. In addition to this 1.8 mg rutin /mL inhibit biofilm formation by 53%.These finding suggest that pummel peel flavonoids can be uses as antibiotic and as quorum sensing inhibitor to overcome drug resistance. (Liu *et al.*, 2017).

Organic acids

The organic acids could be used as quorum sensing inhibitor from fresh fruits and vegetables. The effect

of acetic acid, citric acid and lactic acid on biofilm making and anti QS potential was also determined. Maximum blocking of biofilm manufacturing was noted at 39% with lactic acid in *E.coli* and a minimum of 22% with citric acid in *Salmonella sp*.Exopolysaccharide (EPS) formation was effected in *E coli* with lactic acid showing decline by 13% while citric acid and acetic acid demonstrate only 6% and 10% correspondingly. Lactic acid and acetic acid display higher Anti QS ability when contrast with citric acid. 2 % lactic acid application on cucumber had shown that it was effective in inhibiting growth of *E.coli* and *Salmonella sp*. Thusabove acids are efficient disinfectants in declining the bacterial growth related with fresh fruits and vegetables (Amrutha *et al*., 2017).

Essential oils

The preservatives which are used to check biofilm gave lot of safety issues. For that purpose essential Oils (EOs) usually considered as safe product. The objective of current work to determine the chemical composition and then pathogenic properties of essential oils against *Pseudomonas aeruginosa*.Essential oils contain highest amount of monoterpene hydrocarbons. The essential oils were unable to inhibit growth of bacteria at 4.1mg/ mL.butessential oils inhibited the growth of biofilm in *Pseudomonasaeruginosa* at 0.1 mg/mL. ES also check biofilm cell viability 41%, acyl homoserinelactone formation 33%, and consequently more than 77% reduction in elastase activity. Hence Citrus reticulata EOs are appropriate choice to chemical additives for common use in the food manufacturing (Luciardi *et al*., 2016).

Meliadubia

E coli are the most common pathogen of the Urinary track and almost evolve in 90% of cases of UTI. SdiA, a quorum sensing regulator is well known to direct the behavioral changes of uropathogen*E. coli* in setting up biofilm and virulence. So researcher hypothesized that the selective inhibitor of SdiA which is derived from plant *Meliadubia*would a remarkable candidate to down regulate the uropathegen biofilm and virulence factors. In this study fructose-Furoic acid ester had been prepared and characterized and then it was observed that it effectively check the biofilm formation in *E.coli*. Genetic studies using qRT-PCR showed that controlling the quorum sensing regulated genes (*fimA, csgA, espA)*. It had been find out that about 70 different bacterial species use SdiA system to control their communication. Thus this compound could be further develop as broad spectrum antibiotic medicine (Vinothkannan *et al*., 2018).

Fusaricacid

Fusaric acid and 39 analogues had being manufactured by taking benefit of microwave. The fusaric acid analogue were evaluated by using microtiter plate screening method for inhibition of *las*and *rhl*QS system in *Pseudomonas aeruginosa* the Lux QS system in *Vibrio fischeri*. 8 compounds out of 40 analogues of fusaric acid checked *lux* QS system. And one compound had shown inhibition against *las* QS system. To our amusement none of the compounds had shown no growth inhibitory effect on tested strains (Tung, *et al*., 2017).

Flash nanoprecipitation

Pseudomonas aeruginosa is a stubborn pathogen which usually difficult to treat. Strategies that can reduce *P. aeruginosa* infections without provoking resistance could alter how *P.aeruginosa* infections are handled. In this study Flash Nanoprecipitation (FNP) to inventnewgeneration quorum sensing therapeutics that function by reducing *P.aeruginosa*virulence without killing bacteria. Problem for the delivery of QS drugs such as poor water solubility and failure to pierce through pulmonary mucus to reach sites of infection, are improved when process into nanocarriers (NC) form through FNC. Construct from these techniques are totally water soluble and quickly break through mucus (Lu *et al*., 2018).

While V-06-18 reduces activity of LasR, other signaling agents that disperse biofilm may be in the same way important to co-deliver with QS agents that

decrease virulence (Muh *et al.,* 2006). The dispersal of biofilm make microbe more vulnerable to antibiotic drugs. Therefore co-encapsulation of multiple actives is easily achieved by FNP (Pinkerton *et al.*, 2015).

Resveratrol

In view of the essential role of quorum sensing in *Psuedomonasaeruginosa* infection, the boosted effect between the quorum sensing inhibitor resveratrol and several antibiotics against *P.aeruginosa* were examined. Staining Assay disclosed that the biofilm of *P.aeruginosa* developed in the presence of resveratrol were more vulnerable to aminoglycoside antibiotics. FL-SEM showed structural disturbance of the biofilm when treated with resveratrol and aminoglycoside. Further analysis confirmed that genes LasI and rhll, that formed signal molecules in QS system, were inhibited in the *P.aeruginosa* biofilms by resveratrol. These results showed that QSI inhibitors can appreciably enhance the effect of aminoglycoside antibiotics against *P.aeruginosa*. These results showed that resveratrol is a potent accelerant in the managementof*P.aeruginosa* biofilm and can reinstate the potency of aminoglycoside (Zhou*, et al.,* 2018).

Conclusion

In last twenty years, scientist finds out that how microbes communicate with each other and how this communication helps bacteria to control their pathogenic behavior. Novel compounds and their effect on bacterial pathogenic behavior are still being revealed. It is confirmed now that the link of QS and pathogenesis shows potential region from which new drugs are formulated Further research is needed to fully understand how these compound control virulence factors, how much these QSIs compounds have to face the problem of resistance in bacteria and what should be the ideal dose to inhibit Quorum sensing in microbes.

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