Chapter 20
Quorum Sensing Interference by Natural Products from Medicinal Plants: Significance in Combating Bacterial Infection

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Abstract Plant derived natural products and phytocompounds are known for their broad spectrum biological activities and are of great therapeutic value in traditional system of medicine. The role of medicinal plants and phytocompounds in the treatment of various diseases including bacterial infection are widely documented. Anti-infective compounds from medicinal plants may provide new drug leads. Bacterial cell to cell communication has been become attractive target for the development of novel anti-infective measures that do not rely on the use of antibiotics. Targeting Quorum sensing has been emerge as promising strategy to combat bacterial infections as it is unlikely to develop multidrug resistance pathogens since it does not impose any selection pressure. In this review, we have surveyed the recent literature available on plant extracts, essential oils and phytocompounds exhibiting anti-quorum sensing properties. Further, significance of phytocompounds to combat bacterial infections caused by MDR bacteria has been discussed.

Keywords Anti-QS activity · Autoinducer · Bacterial cell to cell communication · Infectious disease · *N*-acylhomoserine lactone · Medicinal plants · Phytocompounds

Abbreviations

AHL	N-Acyl homoserine lactone
AI	Auto Inducer
CF	Cystic Fibrosis
EPS	Extracellular Polymeric Substances

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HSL Homoserine Lactone
MDR Multi Drug Resistance
MIC Minimum Inhibitory Concentration
QSI Quorum Sensing Inhibitors

20.1 Introduction

Infectious diseases are one of the major cause of mortality and morbidity. The development of multi antibiotic resistance among pathogenic bacteria has created immense clinical problem. Development of new antibacterial drugs with novel mechanism of action and use of new treatment strategies is urgently needed to combat the problem of infection caused by MDR-bacteria. Targeting virulence and pathogenicity is one of such strategy (Aqil et al. 2006).

Density dependent, small diffusible signal mediated gene regulation system in bacteria, that controls expression of virulence traits is termed as "Quorum sensing". These small diffusible signal molecules or autoinducers allows bacteria to regulate expression of large sub-set of genes related to pathogenicity with change in bacterial population (Camara et al. 2002). This signalling system has distinct architecture necessary for signal dissemination, revelation and response and has been well characterized in Gram-negative and Gram-positive bacteria (Miller and Bassler 2001; Lazdunski et al. 2004). Dismantling QS networks without having toxicity on target bacteria is considered as one of the important alternative strategy for combating bacterial infections with advantageously decreasing the risk of selection pressure (Bjarnsholt and Givskov 2007; LaSarre and Federle 2013). Thus identification, characterization and development of effective quorum sensing inhibitors (QSI) considerably gain attention from scientific community worldwide as a promising remedy to combat infection caused by multi-resistance bacteria. A potential QSI would have act through three possible mechanisms, (**a**) targeting the signal generation, (**b**) degradation of signal molecule and/or by (**c**) blocking the signal receptors. A model QSI having potential to be transformed into successful anti-infective drug should be attributed with high target specificity and negative toxicity towards the target bacterium as well as the eukaryotic host (Rasmussen and Givskov 2006; Ahmad et al. 2011; Kalia 2013; LaSarre and Federle 2013).

Despite of remarkable development in combinatorial chemistry for providing wide range of lead molecules, naturally occurring plant products are still considered as preferred choice in pharmaceutical industry (Silva et al. 2016). Considering the extensive use of plants for medicinal and dietary purposes in human, efforts have been focussed towards plants and their derived products to explore potential therapeutic principles. Plants and their derived natural products represent a vast, unexplored and comparatively safe reservoirs of diverse bioactive compounds

(Atanasov et al. 2015). These plant secondary metabolites spanning from simple phenols to highly diverse terpenes are involve in various biological process relating to plant defence against pathogens, assisting central metabolic processes, response against external stimulants etc. (Koh et al. 2013; Yarmolinsky et al. 2015). Interestingly, many plants products/phytochemicals offer entirely different mechanism of actions when compare to conventional antibacterial, representing an effective alternative to aging antibiotics (Cegelski et al. 2008; Nazzaro et al. 2013). Besides, plants derived natural products plays indispensable role in traditional medicine system worldwide including Chinese, Indian, and other folk medicine, thus research focussing plants derived products would help in bridging the gap between traditional wisdom and modern therapeutics (Adonizio et al. 2006; Ahmad et al. 2011; Zahin et al. 2010a). Role of medicinal plant products and phytocompounds against infectious agents and their diverse mode of action have been investigated and reviewed by several workers (Cowan 1999; Aqil et al. 2006; Palombo 2011; Husain and Ahmad 2013; Silva et al. 2016).

In this chapter, we present an update and brief review on anti QS activity of plants and its derived products including phytocompounds. We systematically covered plant derived natural products including plant extracts (crude or enriched), essential oils and phytocompounds, highlighting their anti-quorum sensing potential along with underlying their mechanism of actions. In the later sections, while addressing the significance of plant based QSI against infectious disease, an attempt have been made to highlight the development of successful plant based QSI that could possibly be used as anti-infective agent for management bacterial infections.

20.2 Plant Extracts with Anti QS Activity: A Recent Update

Studies in past have reported the ability of the plant extracts used in dietary or therapeutic purposes to interfere in intra and inter species QS communication. Plants are considered as vast reservoirs of bioactive chemicals and enzymes which could be act as natural quorum sensing inhibitors. The co-existence of bacteria and plant date back to millions of year which significantly results in the development and evolution of defensive mechanism against pathogenicity primarily involving the disruption of molecular communication. Among the natural strategies unfolded during past investigations includes enzymatic degradation of QS signals, the inhibition of autoinducer synthesis, receptor antagonism and disruption of signal secretion. However, recent advances in the field of plant based QSI research are more specifically focused on gene expression variation along with targeting global regulatory factors controlling overall QS mechanism. Table 20.1 shows list of common dietary and medicinal plants which have demonstrated QS inhibitory activity.

Table 20.1 Anti-QS activity of dietary and medicinal plants

Plant name	Part used for extraction	Biosensor strain(s) used	Virulence factor(s) inhibited	References
Syzygium jambos	Leaves	*C violaceum* DMST 21761	Pyoverdin	Musthafa et al. (2017)
Syzygium antisepticum		*P. aeruginosa* ATCC 27853		
Pelargonium hortorum	Aerial parts	*P. aeruginosa*	Motility	Elmanama and Al-Reefi (2017)
Punica granatum			Pyocyanin	
Artemisia absinthium			LasA protease	
Hibiscus sabdariffa				
Momordica charantia				
Forsythia suspense	Aerial parts	*C. violaceum* ATCC 12472	Pyocyanin, Protease, biofilm and motility	Zhang and Chu (2017)
		P. aeruginosa		
Amomum tsaoko	Fruit pods	*C. violaceum*	Pyocyanin, biofilm and motility	Rahman et al. (2017)
		P. aeruginosa		
Pistacia atlantica	Leaves	*P. aeruginosa* PA01	Pyocyanin	Kordbacheh et al. (2017)
Astilbe rivularis	Leaves	*C. violaceum* MTCC 2656	Pyocyanin and swarming motility	Tiwary et al. (2017)
Fragaria nubicola		*P. aeruginosa* MTCC 2297		
Osbeckia nepalensis				
Piper betle	Leaves	*V. harveyi* MTCC 3438	EPS, swimming motility and biofilm	Srinivasan et al. (2017)
Terminalia bellerica	Leaves	*C. violaceum* ATCC 12472	EPS, pyocyanin and biofilm	Ganesh and Rai (2017)
		P. aeruginosa PA01		
Salvadora persica	Fruit and leaves	*C. violaceum* ATCC 12472	Violecein	Noumi et al. (2017)
		C. violaceum CV026		
Cassia alata	Leaves	*C. violaceum* ATCC 12472	Swarming motility, pyocyanin, LasB elastase, protease and biofilm	Rekha et al. (2017)
		C. violaceum CV026		
		C. violaceum ATCC 31532		
		P. aeruginosa PAO1		
Mangifera indica	Leaves	*C. violaceum* ATCC 12472	Elastase, protease, pyocyanin, EPS, chitinase, swarming and biofilm	Husain et al. (2017)
		P. aeruginosa PAO1		

(continued)

Table 20.1 (continued)

Plant name	Part used for extraction	Biosensor strain(s) used	Virulence factor(s) inhibited	References
Vaccinium macrocarpon	Fruit	*P. aeruginosa* PA14 QS mutants	Elastase (LasA and LasB), alkaline protease	Maisuria et al. (2016)
		C. violaceum ATCC 31532		
Euodia ruticarpa	Fruit	*C. jejuni* NCTC 11168 QS mutants	Luminescence and biofilm formation	Bezek et al. (2016)
		V. harveyi BB 170		
Punica granatum	Peel	*C. violaceum*	Violecein and biofilm	Yang et al. (2016)
Eugenia brasiliensis	Fruit	*C. violaceum* ATCC6357	Violecein and swarming motiliy	Rodrigues et al. (2016a)
Eugenia Uniflora	Fruit	*C. violaceum ATCC6357*	Violecein	Rodrigues et al. (2016b)
Glycyrrhiza glabra	Root	*C. violaceum* ATCC 12472	Violecein	Cosa et al. (2016)
Apium graveolens	Leaves & Stalk			
Capsicum annuum	Fruit			
Syzygium anisatum	Seed			
Anogeissus leiocarpus	Stem bark	*C. violaceum* CV026	Pyocyanin and violecein	Ouedraogo and Kiendrebeogo (2016)
		P. aeruginosa PAO1 QS mutants		
Berberis aristata	Stem bark	*E. coli* (Isolated)	Adhesion and biofilm	Thakur et al. (2016)
Camellia sinensis	Leaves			
Holarrhena antidysenterica	Stem			
Piper betle	Leaves	*S. marcescens* (Isolted)	Protease, lipase, biofilm, swarming motility and EPS	Srinivasan et al. (2016)
Acer monspessulanum	Leaves	*C. violaceum* ATCC 12472	Violecein and swarming motility	Ceylan et al. (2016)
		C. violaceum CV026		
		P. aeruginosa PAO1		
Syzygium cumini	Fruit	*C. violaceum* CV026	Violecein	Gopu et al. (2015b)
Rubus rosaefolius	Fruit	*C. violaceum* ATCC6357	Violecein, biofilm and swarming motility	Oliveira et al. (2016)

(continued)

Table 20.1 (continued)

Plant name	Part used for extraction	Biosensor strain(s) used	Virulence factor(s) inhibited	References
Trigonella foenum-graceum	Seed	*C. violaceum* ATCC 12472 *C. violaceum* CV026 *P. aeruginosa* PAO1	Elastase, protease, pyocyanin, EPS, chitinase, swarming and biofilm	Husain et al. (2015a, b)
Adenanthera pavonina	Leaves	*C. violaceum* ATCC 12472 *C. violaceum* CV026 *P. aeruginosa* PAO1	Elastase, protease, pyocyanin, swarming and biofilm	Vasavi et al. (2015)
Hyptis suaveolens	Leaves	*C. violaceum* ATCC 12472	Protease, heomolysin, swimming and swarming motility	Salini et al. (2015)
Nymphaea tetragona	Leaves & Stalk	*C. violaceum ATCC 12472* *C. violaceum CV026* *P. aeruginosa PAO1*	Swarming motility, pyocyanin, biofilm and LasA protease	Hossain et al. (2015)
Psidium guajava	Leaves	C. violaceum MTCC 2656 *P. aeruginosa* MTCC 2297	Violecein and swarming motility	Ghosh et al. (2014)
Ficus carica *Perilla frutescens*	Leaves	*C. violaceum* CV026 *P. aeruginosa* PAO1	Violecein and swarming motility	Sun et al. (2014)
Citrus limon *Citrus medica* *Citrus aurantium*	Peel	*C. jejuni* NCTC 11168 *V. harveyi* BB170	Swarming motility and biofilm	Castillo et al. (2014)
Kigelia africana	Fruit	*C. violaceum* ATCC 12472 *A. tumefaciens* A136, KYC6	Violecein	Chenia (2013)
Fructus gardenia *Andrographis paniculata*	Whole plant	*C. violaceum* ATCC 12472 *P. aeruginosa* PAO1	Protease, elastase, pyocyanin, swimming motility and biofilm	Chu et al. (2013)
Dalbergia trichocarpa	Bark	*P. aeruginosa* PAO1 QS mutants	Pyocyanin, LasB, protease, biofilm and swarming motility	Rasamiravaka et al. (2013)

20.2.1 Dietary Plants

Recently, extracts of different botanical groups of dietary plant including fruits, vegetables and culinary herb and spices have been demonstrated as strong QSI (Table 20.1). Primarily, fruits received special attention, as they are important part of diet and exert beneficial effects on human health. Fruit extracts, owing to their rich dietary phytochemical content, have been recognized as promising source in the search of novel anti-infective (Truchado et al. 2015).

Aqueous extract of fruits of *Ananas comosus* (pineapple) and *Manilkara zapota* (sapodilla) were found to inhibit the QS system in *Chromobacterium violaceum* CV026 and *P. aeruginosa* PA01, inhibiting QS dependent virulence factors (pyocyanin, staphylolytic protease, elastase and biofilm formation) production (Musthafa et al. 2010). Apple extract when evaluated for QS inhibition against *C. violaceum*, showed a dose-dependent inhibition in pigment production (Fratianni et al. 2011). Koh and Tham (2011) showed that extract of *Prunus armeniaca* (apricot) inhibits AHL production in *C. violaceum* CV026 biosensor strain as well QS dependent swarming motility in *P. aeruginosa* PA01. Quorum sensing regulated production of AHLs and biofilm formation in *Yersinia enterocolitica* was found to be inhibited by flavonones rich orange extract (Truchado et al. 2012).

Berries are considered as rich source of phenolic phytochemicals such as flavonoids including anthocyanins, flavanols and flavonols, tannins, stilbenoids, phenolic acid and lignans (Vattem et al. 2007). It was observed that the production of AHL and AI-2 signal molecule was depleted under the influence of extracts of three berries when tested with *C. violaceum* CV026 and *Vibrio harveyi* BB170 tester strains and the effect was found to be concentration dependent. These phenolic rich extracts of raspberry and cloudberry also caused significant reduction of biofilm formation of *Obesumbacterium proteus* (Priha et al. 2014). Similarly, phenolic extracts of *Rubus rosaefolius*, a berry indigenous to Himalayan region of South Asia, inhibited all the phenotypes typically related to quorum sensing including violacein production, swarming motility and biofilm formation in *C. violaceum*, *Aeromonas hydrophila* and *Serratia marcescens.* Authors further observed that QS disruptive principle were predominantly natural phenols (Oliveira et al. 2016).

Another edible berry, *Syzygium cumini*, derived anthocyanin rich extracts examined for the anti-QS potential against different QS linked phenotypes in *C. violaceum* and *Klebsiella pneumoniae*. Anthocyanin constituent, malvidin, was found to interrupt the QS mechanism via binding with LasR regulatory protein as revealed from docking studies. Malvidin was also shown to inhibit virulence determinants e.g. biofilm formation and EPS (extracellular polymeric substances) production in *K. pneumoniae* (Gopu et al. 2015a). Phenolic rich extracts from Brazilian berries *Eugenia brasiliensis* and *Eugenia uniflora* have been confirmed for their quorum quenching capacities using *C. violaceum* biosensor strain (Rodrigues et al. 2016a, b). Moreover, the phenolic extract of grumixama (*Eugenia brasiliensis*) inhibited the QS regulated swarming motility in *A. hydrophila* and *S. marcesens* at concentra-

tion non-inhibitory to bacterial growth. Authors hypothesize that the observed QS inhibitory potential of the extract may have related to its phenolic constituents which have act synergistically or individually, producing the biological effect (Rodrigues et al. 2016a). Maisuria and co-workers (2016), evaluated the proanthocyanidins rich extract of cranberry (*Vaccinium macrocarpon*) against QS-linked virulence traits of *P. aeruginosa* in host *Drosophila melanogaster*. It was observed that application of the extract inhibited the production of virulence determinants and subsequently protected the host organism from fatal infection of *P. aeruginosa.* LC-MS analysis of culture supernatant revealed that levels of autoinducers (AHL) was depleted significantly. QS signalling genes including AHL synthesase LasI/RhlI and transcriptional regulators LasR/RhlR were also inhibited by proanthocyanidins rich extract. Additionally, *in silico* molecular modelling suggested that proanthocyanidins binds to QS transcriptional regulatory proteins, ultimately refraining the ligand molecules (autoinducers) to bind with active sites.

Herbs and spices are also considered as rich source of bioactive phytochemicals and extensively used in various food preparations as well as ethno-pharmaceuticals. Latest reports regarding biological activity prospect of these herbs and spices highlight their anti QS and anti-virulence potential (Table 20.1). Makhfian et al. (2015) screened 31 plant species including numerous spices and herbs for analysing their inhibitory potential against QS related behaviours, violacein pigment production in *C. violaceum* CV026 and plant tissue maceration caused by *Pectobacterium carotovorum*. Among them, the dill (*Anethum graveolens*) extract demonstrate AHL mimicking activity and subsequently inhibit violecein production to significant levels. Moreover, the extract was also effective against *Pectobacterium carotovorum* mediated tissue maceration in potato tubers and calla-lily slices. *Trigonella foenum-graceum* seed's (commonly known as fenugreek) methanol extracts demonstrated inhibition of AHL regulated virulence factors e.g. protease, LasB, elastase, pyocyanin, chitinase, EPS and swarming motility in *P. aeruginosa* PA01 and PAF79 as well as QS regulated swarming motility in aquatic pathogen *A. hydrophila* WAF38. Further, the application of the bioactive extract subsequently downregulate lasB gene as evident from β-galactosidase luminescence in *E. coli* MG4/pKDT17. Additionally, *in vivo* infection model (*Caenorhabditis elegans*), the extract exhibit significant reduction in mortality rate in infected nematode. Caffeine was identified as a major volatile constituent in the extract, also showed significant reduction in QS regulated virulence traits including biofilm formation in pathogenic bacteria (Husain et al. 2015a).

Plant derived beverages including tea and coconut water have been also found to be effective against pathogenic bacteria via modulating their QS related response. Tea polyphenols interfered with autoinducers (AI-2 and diketopiperazines) activities of *Shewanella baltica*, promoted the degradation of AI-2 and was found to be function of epigallocatechin gallate constituent of the extract. Reduction in QS phenotypes such as biofilm development, swarming motility and exopolysaccharide production were suggested to be linked with downregulation of luxS and torA genes as revealed from transcriptional analysis (Zhu et al. 2015). Two-furaldehyde diethyl

acetal (2FDA) was identified as potential QSI by screening of identified compounds from water of *Coccus nucifera* via molecular docking studies using transcriptional regulator proteins LasR and RhlR as target. Subsequent transcriptional analysis revealed down regulation of autoinducer genes (lasI/rhlI) and transcriptional regulator genes (lasR/rhlR) that corresponds to observed reduction in QS regulated traits including biofilm formation, aeruginolysin, LasA, LasB, elastase, protease, swarming motility, pigment and haemolysin production in *P. aeruginosa*. Authors also demonstrated the synergistic activity of palmitic acid, another bioactive constituent obtained from coconut water, increases overall QS inhibitory and antibiofilm potential of 2-FDA (Sethupathy et al. 2015). Celery (*Apium graveolens*) leaf's extract was found to inhibit pigment production in *C. violaceum* at significant levels, however other spices under the examination such as *Syzygium anisatum*, *Glycyrrhiza glabra* and *Capsicum annuum* showed moderate activity. The active constituent 3-n-butyl-4,5-dihydrophthalide (sedanenolide) was isolated from *Apium graveolens* extract and identified using preparative HPLC-MS followed by LC-ToF-MS analysis (Cosa et al. 2016).

20.2.2 Medicinal Plants

Apart from food plants, abundant accounts of quorum sensing inhibitory activity were also reported from medicinal plants. Ethnobotanical use of plants in treatment of various ailment including bacterial infection was one of the important convincing argument which scientific community put forward to direct the search of novel anti-infective or more precisely anti-QS agent from medicinal plants (Adonizio et al. 2006). With special reference to Indian medicinal plants, first attempt was made in 2006, screening the commonly used medicinal plants for their quorum sensing inhibitory properties (Sameena 2006). Subsequently, studies undertaken by several workers (Fatima et al. 2010; Musthafa et al. 2010; Harjai et al. 2010; Zahin et al. 2010b; Husain et al. 2013; Packiavathy et al. 2014; Tiwary et al. 2017), highlighted that Indian medicinal plants as a potential source of quorum sensing inhibitors.

Till date hundreds of medicinal plant extracts have been shown to exhibit anti-QS potential in one or more screening system (Kalia 2013; Yarmolinsky et al. 2015; Silva et al. 2016; Tiwary et al. 2017). The search of potential QSI from medicinal plants become more considerable keeping in view their long history of human use, thus toxicity issues, at least hypothetically, can be ruled out. Furthermore, this search will also boost the concept of evidence based complementary medicine and shed new light on important biological mechanism through which these plant based non-conventional remedy system works (Kothari et al. 2017). Development of medicinal plants into successful anti-pathogenic alternative will also eliminate the present day's shortcomings with conventional antibiotics including development of resistance apart from other side-effects.

As discussed in earlier sections, owing to their rich, diverse and continuously evolving bioactive chemical source, these plants are considered to most effective

and most important candidate therapeutics. Table 20.1 presents a brief account of recent reports concerning quorum sensing modulatory effect of various medicinal plant extracts.

20.2.3 Essential Oils

Essential oil derived from plants are widely been recognised as flavouring agent and antimicrobials. Their biological efficacy has been attributed to their constiuent phenolics, terpenes and terpenoid volatiles (Bakkali et al. 2008). These essential oils have also been reported to possess anti-QS properties (Khan et al. 2009; Szabó et al. 2010). Table 20.2 summaries some of the recent reports on QS inhibiting potential of essential oils.

Khan et al. (2009) screened 21 commonly used essential using biosensor strains, *C. violaceum* CV12472 and CVO26. Among them, four essential oils, clove, cinnamon, lavender and peppermint oil showed varying level of QS inhibitory effects in a dose dependent manner. Yap and co-workers (2014) highlight the role of QS inhibitory and membrane disruption action of lavender (*Lavandula angustifolia*) oil as possible mechanism for the observed antibacterial effects. The oil was assayed employing two bioluminescence biosensor strains *Escherichia coli* [pSB1075] and *E. coli* [pSB401] and found effective against the LasR receptor containing strain *E. coli* [pSB1075]. While evaluating different chemotype of essential oil obtained from *Lippia alba,* Olivero-Verbel and co-worker (2014) observed that oil containing high ratio of geranial:neral and limonene:carvone were found to be most effective against QS-controlled violacein pigment production. Moreover, among the two, geranial/neral chemotype was also found effective against *Staphylococcus aureus*. Sub-lethal concentrations of cinnamon oil were found reduce the production of both short and long chain AHL molecules as evident from CV026 and PA01 bioassay. Subsequently, the lower levels of AHL signals were also found in relationship with observed inhibition of pyocyanin, swarming motility, alginate and total exoprotease activity in PA01. Authors suggested that cinnamaldeyde, a major volatile constituent of cinnamon oil could be responsible for observed anti QS activity, nonetheless, other constituent such as eugenol may synergistically or solitary targeted the QS circuit in the tested bacterium (Kalia et al. 2015).

Coriander essential and its major constituent were shown to significantly inhibit the biofilm formation in *Campylobacter jejuni* and *Campylobacter coli.* The oil and its major component linalool also demonstrate inhibitory effects against the production of QS-controlled violecein pigment in *C. violaceum* biosensor strains. Authors concluded that observed anti biofilm activity against the food borne pathogen could possibly the outcome of quorum sensing disruption (Duarte et al. 2016). Luis and co-workers (2016) evaluate anti-QS properties of two eucalypt essential oils namely *E. radiata* and *E. globulus* containing limonene and eucalyptol as major constituent respectively. *E. Radiate* was shown to exhibit greater QS interfering potential.

Table 20.2 Anti-QS activity of essential oils

Source plant	Family	Major component (s)	References
Ellettaria cardamomum	Zingiberaceae	α-terpinyl acetate, 1.8-cineole, Linalool acetae, sabinene	Asghar et al. (2017)
Coriandrum sativum	Apiaceae	Linalool	Duarte et al. (2016)
Thymus vulgare	Lamiaceae	Carvacrol, and thymol	Myszka et al. (2016)
Eucalyptus globulus	Myrtaceae	Eucalyptol	Luis et al. (2016)
Eucalyptus radiata		Limonene	
Citrus reticulata	Rutaceae	Limonene,	Luciardi et al. (2016)
Cryptocaria massoia	Lauraceae	Massoialactone	Pratiwi et al. (2016)
Murraya koenigii	Rutaceae	Caryophyllene, caryophyllene oxide, cinnamaldehyde, α- and β-phellandrene	Ganesh and Rai (2016) and Bai and Vittal (2014)
Ferula asafoetida	Apiaceae		Sepahi et al. (2015)
Dorema aucheri Boiss			
Mentha piperita	Lamiaceae	Menthol	Husain et al. (2015a, b)
Aloysia triphylla	Verbenaceae	Z-citral and E-citral	Cervantes-Ceballos et al. (2015)
Cymbopogon nardus	Poaceae	Citronellal, geraniol, citronelol	
Lippia origanoides	Verbenaceae	trans-β-caryophyllene, p-cymene, Limonene	
Hyptis suaveolens	Lamiaceae	Sabinene, β-caryophyllene, terpinolene, β-pinene	
Swinglea glutinosa	Rutaceae	β-pinene, α-pinene, sabinene	
Eucalyptus globulus	Myrtaceae	1.8-cineole, α-pinene	
Cinnamomum verum	Lauraceae	Cinnamaldehyde	Ganesh and Rai (2015) and Kalia et al. (2015)
Lavandula angustifolia	Lamiaceae	Linalyl anthranilate and linalool	Yap et al. (2014)
Lippia alba	Verbenaceae	Limonene, neral, carvone, geraniol, bicyclosesquitelandrene	Olivero-Verbel et al. (2014)
Minthostachys mollis	Lamiaceae	Pulegone and D-Menthene	Pellegrini et al. (2014)

(continued)

Table 20.2 (continued)

Source plant	Family	Major component (s)	References
Rosa damascene	Rosaceae	Citrenellol, geraniol, nonadekan	Eris and Ulusoy (2013)
Matricaria recutita	Asteraceae	Lillyl aldehyde, geraniol, linalool	
Eugenia caryophyllata	Myrtaceae	Propylene glycol, eugenol	
Pinus sylvestris	Pinaceae	α-pinene, β-pinene, limonene	
Syzygium aromaticum	Myrtaceae	Eugenol	Husain et al. (2013) and Khan et al. (2009)

Citrus reticulate essential oils and limonene, a cyclic monoterpene, have been shown to decrease the autoinducer (AHL) reduction levels by 33% as evident from *P. aeruginosa* qsc 119 bioreporter strain, and subsequently decreasing the elastase enzyme in *P. aeruginosa* HT5 by 75%. However, authors suggested, as revealed by the relationship between elastase production and AHL inhibition, that overall reduction in enzymatic activity was not only due to QS disruption, but also because of direct inhibitory effect of essential oils and its component on the enzyme activity (Luciardi et al. 2016). Pratiwi et al. (2016), while investigating the quorum quenching effect of *Cryptocaria massoia* essential oil observed that the oil effectively impeded the QS-dependent swarming motility of *P. aeruginosa* PA01 and violacein reduction in *C. violaceum* CV026 biosensor. Similarly, *Ferula asafoetida* and *Dorema aucheri* essential oil have also been found to be active against *P. aeruginosa* associated virulence factors including pyoverdine, pyocyanin, elastase and biofilm at significantly low concentration (25 μg/ml). Homoserin lactones (HSL) inhibition and down regulation of QS related genes were considered as apparent mode of action of the oils as observed from *in vitro* assessments. Additionally, keeping in view the diverse of chemical composition of the oil, authors speculated that multiple QS associated molecular target might be affected or global regulator like Vfr or GacA might be impeded (Sepahi et al. 2015). Bai and Vittal (2014) and Ganesh and Rai (2016), independently evaluated the quorum sensing inhibitory activity of essential oil of *Murraya koenigii* and found to be active against AHL mediated cell communication. Biofilm formation, cell attachment, EPS production and biofilm maturation by *P. aeruginosa* were shown to be attenuated at sub-MICs of the oil. Food spoilage by psychotropic *P. psychrophila* PSPF19 was also found to be delayed under the influence of the oil and related to its observed anti-QS activity (Bai and Vittal 2014). Ganesh and Rai (2016) examined the antipathogenic efficacy of *Murraya koenigii* essential oil *in vivo* using nematode *C. elegans–Pseudomonas aeruginosa* infection model. Along with rescuing 60% of *C. elegans*, the oil was also shown to inhibit other virulence factors such as pyocyanin and LasA staphylotic activity significantly. Asghar et al. (2017), demonstrated the activity of *Elletaria cardamomum* (zingiberaceae) essential oil against the pigment production

in *C. violaceum* at the concentrations non-inhibitory to bacterial growth. Authors suggested that volatile components of the oil such as α-terpinyl acetate, 1,8-cineole, linalool acetate etc., could be responsible for the observed biological effect.

20.3 Plant Derived Phytocompounds as QSI

Different plant based chemical molecules comprising of diverse chemical groups including flavonoids, fatty acid derivatives, alkaloids, coumarins, lignans, terpenoids etc., have been identified as potent anti-quorum sensing agent (Nazzaro et al. 2013; Silva et al. 2016; Asfour 2017). Recent reports on bioactive photochemicals against QS mechanism and chemical structures has been presented in Table 20.3 and Fig. 20.1. A brief description of some of important chemical groups is presented as follows.

Table 20.3 Anti-QS activity and mode of actions of plant derived phytocompounds

Phytocompound	Source plant(s)	Test organisms	Mode of action	References
Naringenin	*Combretum albiflorum*	*Pseudomomas aeruginosa* PA01	**1.** Reducing the production of signal molecules **2.** Affecting the proper functioning of signal-receptor complex	Paczkowski et al. (2017) and Vandeputte et al. (2011)
Diarylheptanoids	*Alnus viridis* *Alnus glutinosa*	*Pseudomonas aeruginosa*	Reducing the production of signal molecules	Ilic-Tomic et al. (2017)
Tannic acid	(Pure)	*Aeromonas hydrophila*	Down regulating the expression of QS related genes	Patel et al. (2017)
Zeaxanthin	(Pure)	*Pseudomonas aeruginosa*	Down regulating the expression of QS related genes	Gökalsın et al. (2017)
Carvacrol and thymol	*Thymus vulgare*	*Pseudomonas fluorescens* *Pseudomonas aeruginosa*	Reducing the production of signal molecules	Myszka et al. (2016) and Tapia-Rodriguez et al. (2017)
Eugenol	*Syzygium aromaticum*	*Pseudomonas aeruginosa*	Down regulating the expression of QS related genes	Al-Shabib et al. (2017) and Zhou et al. (2013)
Petunidin	(Pure)	*K. pneumoniae*	Inhibiting receptor protein	Gopu et al. (2016)

(continued)

Table 20.3 (continued)

Phytocompound	Source plant(s)	Test organisms	Mode of action	References
Baicalein	*Scutellaria baicalensis*	*Staphylococcus aureus*	Down regulating the expression of QS related genes	Chen et al. (2016)
Rosmarinic acid	(Pure)	*Aeromonas hydrophila*	Down regulating the expression of QS related genes	Rama Devi et al. (2016)
Phytol	*Piper betle*	*Serratia marcescens*	Down regulating the expression of QS related genes	Srinivasan et al. (2016)
Linalool	*Coriandrum sativum*	*Acinetobacter baumannii*		Alves et al. (2016)
Quercetin	(Pure)	*Pseudomonas aeruginosa*	Mimicking the QS signal	Gopu et al. (2015b) and Paczkowski et al. (2017)
Quercetin	(Pure)	*Candida albicans*	Inhibiting the protein involve in quorum sensing	Singh et al. (2015)
Flavonoid rich fraction	*Glycyrrhiza glabra*	*Acinetobacter baumannii*	Inhibiting the expression of QS related genes	Bhargava et al. (2015)
Menthol	*Mentha piperita*	*Pseudomonas aeruginosa*	Inhibiting receptor protein	Husain et al. (2015b)
Zingerone	*Zingiber officinale*	*Pseudomonas aeruginosa*	Inhibiting receptor protein	Kumar et al. (2015)
Oxyresveratrol	*Smilax china*	*Pseudomonas aeruginosa*	–	Sheng et al. (2015)
Tea polyphenols	*Camellia sinensis*	*Pseudomonas aeruginosa*	–	Yin et al. (2015)
6-Gingerol	*Zingiber officinale*	*Pseudomonas aeruginosa*	Down regulating the expression of QS related genes	Kim et al. (2015)
Methoxy flavones and methoxy chalcones	*Piper delineatum*	*Vibrio harveyi*	Disturbing signal transduction.	Martín-Rodríguez et al. (2015)
2-Furaldehyde diethyl acetal	*Cocos nucifera* water	*Pseudomonas aeruginosa*	Down regulating the expression of QS related genes	Sethupathy et al. (2015)
Coumarin		*Pseudomonas aeruginosa*	Down regulating the expression of QS related genes	Gutiérrez-Barranquero et al. (2015)
		Aliivibrio fischeri		
Quercitin, quercetin-3-O-arabinoside	*Psidium guajava*	*Pseudomomas aeruginosa* PA01	–	Vasavi et al. (2014)
		Chromobacterium violaceum		

(continued)

Table 20.3 (continued)

Phytocompound	Source plant(s)	Test organisms	Mode of action	References
Curcumin	*Curcuma longa*	*Vibrio spp.*	–	Abraham et al. (2013) and Packiavathy et al. (2014)
Glycosylflavonoids	*Cecropia pachystachya*	*Chromobacterium violaceum*	–	Brango-Vanegas et al. (2014)
Punicalagin	*Punica granatum*	*S. typhimurium*	Down regulating the expression of QS related genes	Li et al. (2014)
Ellagic Acid Derivatives	*Terminalia chebula*	*Pseudomonas aeruginosa* PA01	Down regulating the expression of QS related genes	Sarabhai et al. (2013)
(*R*)-Bgugaine	*Arisarum vulgare*	*Pseudomomas aeruginosa*		Majik et al. (2013)
Methyl eugenol	*Cuminum cyminum*	*Pseudomonas aeruginosa* PA01, *P. mirabilis, S. marcesence, V. harveyi*	1. Interfering with AHL dependent cell differentiation	Packiavathy et al. (2012)
			2. Inhibiting receptor protein	
Naringin	Citrus fruits	*Yersinia enterolitica*	Reducing the production of signal molecules	Truchado et al. (2012)
Malabaricone C	*Myristica cinnamomea*	*Pseudomonas aeruginosa* PA01	Interfering with receptor protein	Chong et al. (2011)
Catechin	*Combretum albiflorum* Bark	*Pseudomomas aeruginosa* PA01	Mimicking the QS signal	Vandeputte et al. (2010)

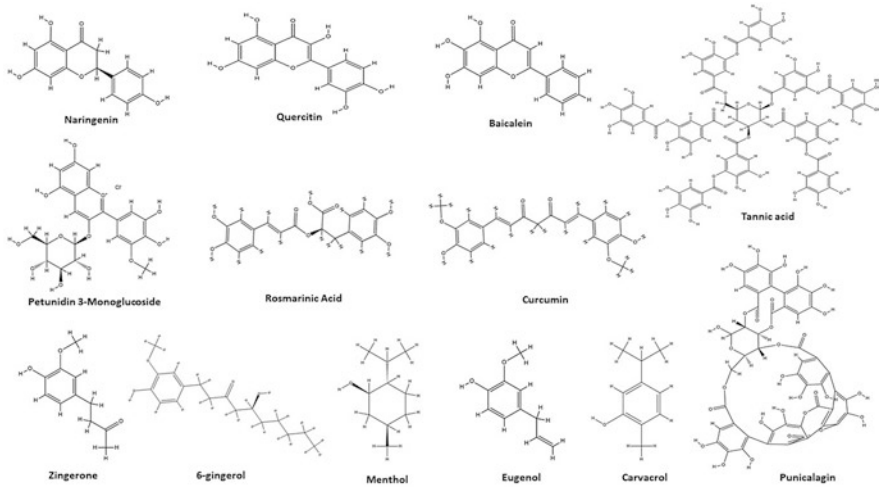

Fig. 20.1 Chemical structures of some of the plant derived QSIs

20.3.1 Flavonoids

Flavonoid, a widely distributed plant secondary metabolites known for their antioxidant and antibacterial efficacy primarily engaged in root elongation process of various plants. These polyphenolic compounds having characteristic benzo-ϒ-pyrene ring are synthesised via phenylproponoid pathway (Kumar and Pandey 2013). Among other pharmacological potentials, this class of plant secondary metabolites have also been shown to possess anti-virulence and anti-QS properties (Paczkowski et al. 2017).

O-glycosylated flavonoids isolated from orange peel including naringin, neohesperidin and hesperidin showed anti QS capacity in *C. violaceum* biosensor strain. These flavonoids were also shown to inhibit QS mediated virulence factors in human enteropathogen *Y. enterocolitica* by decreasing the expression of different genes involves in virulence production (Truchado et al. 2012). Brango-Vanegas et al. (2014) identified numerous flavonoids from *Cecropia pachystachya* Trécul, a widely distributed medicinal plant in Latin America. These C-glycosyl flavonoids such as chlorogenic acid, isoorientin, orientin, isovitexin, vitexin and rutin were shown to act as QS antagonist when screened against *C. violaceum* ATCC 31532 and *E. coli* pSB403 biosensor strains. Two structurally related flavonoids first time isolated from *Piper delineatum* were shown to downregulates the QS regulated bioluminescence in *V. harveyi* reporter strain. These flavonoids broadly classified into methoxy flavones and methoxychalcones groups targets downstream LuxO component in *V. harveyi* at significantly low concentration without affecting the bacterial growth (Martín-Rodríguez et al. 2015). Baicalein (5,6,7-trihydroxyflavone) was shown to reduce the levels of enterotoxin A (SEA) and α-hemolysin (hla) in clinical strain of biofilm forming *S. aureus* (Chen et al. 2016). Notably, baicalein treatment significantly downregulated the quorum sensing regulators *agrA*, RNAIII and *sarA* as well as expression of *ica* gene at sub-inhibitory concentrations (32 and 64 μg/ml). Conformational changes in 3D structure of LasR protein of *K. Pneumonia* was evident on binding with petunidin (flavonoid) and demonstrated using simulation studies (Gopu et al. 2016). Root Mean Square Deviation (RMSD) value of thermal dynamism representing the deviation of 3D structure of LasR–OHL and LasR–petunidin complexes revealed that interaction with petunidin results into closing of active sites of the receptor protein and its further interaction which would otherwise remain open when OHL (auto inducer) molecule was present. The structural activity relationship analysis of different flavonoids reveals that the presence of two hydroxyl groups in the flavone A ring are essential for inhibition of QS related self-regulatory proteins in *P. aeruginosa*. Biochemically it was also established that flavonoids prevent LasR/RhlR-DNA binding non-competitively (Paczkowski et al. 2017). Quercitin, a ubiquitous flavonoids, binds to QS receptor protein LasR and reduce their ability to bind promoter region of DNA thus by down regulating overall expression of QS related genes. Further, Paczkowski et al. (2017) and Gopu et al. (2015b) independently demonstrated that binding of quercetin to receptor protein of *P. aeruginosa* results into conformational changes in the protein structure.

20.3.2 Other Phenolics

Other bioactive phenolic secondary metabolites such as phenolic acids blocks the expression of virulence factors in pathogenic bacterium via modulating QS machinery (Truchado et al. 2012). Truchado and co-workers (2012) evaluated the potential of several food phytochemicals to inhibit QS signals in the biosensor strain *C. violaceum*. A preliminary screening using three different concentrations showed that gallic acid and vanilic acid reduced violacein through QS inhibition. Borges and co-workers (2014) also observed the QSI potential of gallic acid, which inhibited pigment production, although all concentrations tested were cytotoxic to mouse lung fibroblasts. Anti QS properties of coumarin, another polyphenolic compound belongs to benzopyrene class, in three biosensor strains (*S. marcescens*, for short chain AHLs, *C. violaceum* for medium chain AHLs and A. tumefaciens for long chain AHLs) was analysed by Gutiérrez-Barranquero et al. (2015). The compound showed varying level of inhibitory activity against different AHLs and downregulated the expression of QS controlled genes *pqsA* and *rhlI.*

The ability of rosmarinic acid, a phenolic acid predominantly found in members of Lamiaceae family was tested in different pathogenic strains of *A. hydrophila* isolated from infected zebra fish. Rosmarinic acid influenced QS regulated virulence factors such as biofilm formation, haemolysin, lipase and elastase production. Gene expression analysis confirmed the down regulation of virulence genes such as ahh1, aerA etc. It was also observed that *in vivo* treatment of rosmarinic acid in zebra fish infection model subsequently enhances the survival rate (Rama Devi et al. 2016). Tannic acid significantly downregulates Ahyl and AhyR transcript in the tested bacterium as revealed from qRT-PCR results. The phenolic compounds were also tested in *Catla catla* when co-stimulated with pathogenic bacterium (*A. hydrophila*) and shown to decline the extent of pathogen induced skin haemorrhage and enhanced the survival rate up to 86.6% (Patel et al. 2017). Ilic-Tomic and co-workers (2017), examined the QS inhibitory effect of diarylheptanoids isolated from barks of *Alnus viridis,* it was demonstrated that among the isolated diarylheptanoids, hirsutenone was able to inhibit the QS dependent pigment production in *C. violaceum* CV026 and *P. aeruginosa* PA01 along with reduction in the levels of the auto inducer molecule (2-alkyl-4-quinolones) in *P. aeruginosa* PA01.

Among the plant derived pigments, zeaxathin was screened for potential QS inhibitory activity using two *lasB*-gfp and *rhlA*-gfp fluorescent monitor strains of *P. aeruginosa*. Gene expression levels of *lasB* and *rhlA* was observed to decrease in concentration dependent manner. Further, *In silico* modelling approach revealed the significantly favourable stabilizing binding energy of zeaxathin with the active sites of lasB and rhlA. Authors thus suggested that the potential QSI (zeaxathin) imparts its effect via inhibition of regulatory proteins involves in QS circuit (Gökalsın et al. 2017).

20.3.3 Essential Oil's Compounds

Essential oil's compounds, primarily mono-terpenes and sesquiterpenes have been primarily screened for their anti-QS potential against *C. violaceum* and *P. aeruginosa* PA01 bioreporter strains (Ahmad et al. 2015). It was revealed that stereochemical variations among the structurally similar components could be responsible for obtained activity. It has been shown (+)-enantiomers of carvone, limonene and borneol increased violacein and pyocyanin production, on the contrary levo (−) analogs such as a-terpineol and cis-3-nonen-1-ol showed more that 90% inhibition in the pigment production. It was also emphasized that mimicking the autoinducer signals structurally could be considered as possible mechanism of action in virulence inhibition (Ahmad et al. 2015). Two important pungent constituents of ginger oil, 6-gingerol and zingerone were also been investigated to evaluate their ability to interfere with QS and regulated traits in *P. aeruginosa* (Kim et al. 2015; Kumar et al. 2015). Kim et al. (2015) observed that application of 6-gingerol successfully reduced QS regulated virulence factors such as exoprotease, rhamnolipid, biofilm formation etc., in the target bacterium. *In-silico* analysis suggested that the test molecule interfere with the active sites of QS receptor protein lasR via multiple weak interactions. Authors also observed the reduction in QS-induced genes expression under the effect of 6-gingerol thus by confirming the role of 6-gingerol at molecular levels interfering the QS system. Kumar and co-workers (2015), virtually examined the interaction of zingerone with different QS receptors (TraR, LasR, RhlR and PqsR) and observed comparative good docking score to respective autoinducer, thus by proposing zingerone as a promising anti-infective drug candidate. Menthol (5-Methyl-2-(propan-2-yl)cyclohexan-1-ol) has been putatively identified as potent QSI among other component of peppermint oil using molecular docking technique. Further i*n vitro* assessments reveals that menthol significantly reduces expression of QS-controlled traits at sub-MICs in *C. violaceum* and *P. aeruginosa* PA01 in a concentration dependent manner. The addition of menthol to *E. coli* biosensors, MG4/pKDT17 and pEAL08-2 reduced the β-galactosidase luminescence indicating the direct inhibition of *las* and *pqs* transcription respectively (Husain et al. 2015b). Carvacrol and thymol a monoterpenoid phenol was described to inhibit the QS evidently through inhibiting the production of signal molecules (Myszka et al. 2016; Tapia-Rodriguez et al. 2017). In *Pseudomonas fluorescens* KM121biosensor system, carvacrol and thymol were examined for their ability to interfere the production of quorum sensing autoinducers (AHLs) and flagellar gene (*flgA*) expression. Both the components (carvacrol and thymol) of *Thymus vulgare* essential oil significantly modulates the levels of AHLs along with downregulating the expression of motility (flagellar) genes at sub-MIC concentrations (Myszka et al. 2016). Al-Shabib and co-workers (2016), showed that eugenol significantly inhibited the QS regulated violecin production in *C. violaceum* CV026 along with virulence factors in *P. aeruginosa* PA01. Additionally transcriptional regulation assay in *E. coli* MG4/pKDT17 indicates that observed anti QS activity of eugenol is associated with

downregulation of *las* system. Inhibition of QS-controlled production of prodigiosin pigment in *S. marcescens* was observed when treated with sub-inhibitory concentrations of phytol, an acyclic diterpene alcohol isolated from *Piper betle* (Srinivasan et al. 2016). Other related virulence traits including biofilm, hydrophobicity and protease production were also shown to reduce significantly at non-toxic concentration of the volatile component. Alves et al. (2016) screened major components of essential oil of *Coriandrum sativum* including linalool, α-pinene, p-cymene, camphor and geranyl acetate. It was observed that linalool exhibits significant inhibition in the pigment production in *C. violaceum* and QS-dependent bacterial adhesion and biofilm formation in *Acinetobacter baumannii* without affecting the growth of test bacterium.

20.4 Significance of Plant Based QSIs in Combating Bacterial Infection

Development of plant based QSI which can be successfully used as an anti-infective is considered as an ultimate health benefit (Fig. 20.2). Numerous potential plant derived products and synthetic QSIs have been evaluated in animal models (Rumbaugh et al. 1999; Christensen et al. 2007; Nidadavolu et al. 2012). Various animal based *in vivo* models mimicking actual disease conditions like dermonecrosis, lung infection, wound infection, device associated infection and biofilm formation have been developed to test the efficacy of candidate QSI for their possible use in human subjects (Papaioannou et al. 2013). Alternatively, these models can be

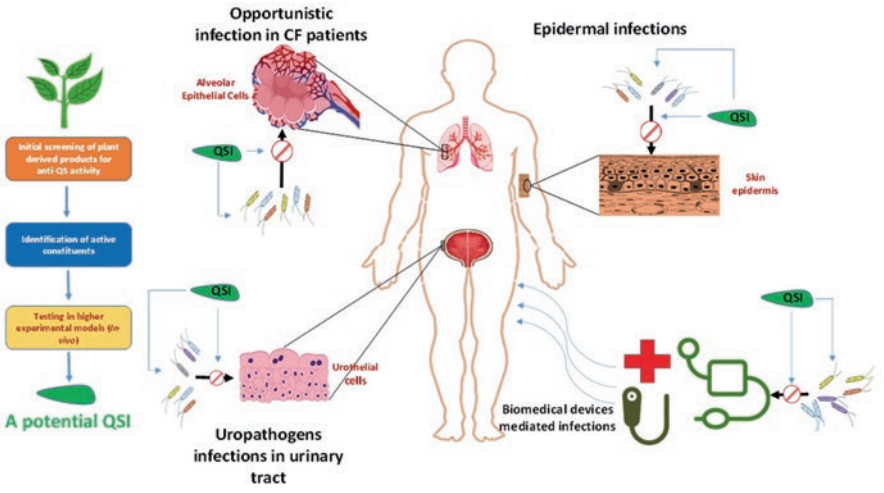

Fig. 20.2 Applications of plant based QSIs in combating bacterial infections

used for validating the use of plants based alternative medicine and substantiate their efficacy with scientific proof. In a study involving mouse infection model and human cell lines, Muhs and co-workers (2017), demonstrate the skin infection treatment ability of *S. terebinthifolia*, an exotic South American weed used locally for treatment of skin infection. The flavone rich active fraction obtained from the plant was shown to possess anti-virulence ability against *S. aureus* via modulating the bacterial *agr* quorum sensing system. The fraction was shown to be well tolerated by human keratinocytes in cell culture and mouse skin *in vivo*. The fraction also inhibited virulent MRSA mediated dermonecrosis in mouse skin model. Baicalin, one of the major flavonoid isolated from roots *Scutellaria baicalensis* have been shown to strengthen the immune response against *P. aeruginosa* infection in mouse model. During preliminary investigation, baicalin was evaluated against different virulence factors including biofilm formation in *P. aeruginosa* and was found be effective in a concentration dependent manner. The authors further observed QSI application results in overall improvement in immune response which was marked by the decrease in interleukin (IL-4) levels, increase in interferon (IFN-ϒ) and reversing interlukin/interferon ratio thus by activating Th-1 induced immune response in the infected host (Luo et al. 2017). Ruffin et al. (2016), observed that LasB and LasA protease secreted by *P. aeruginosa* in airways of patients with CF or other lung disease could further hamper the ability of epithelia to repair. Authors demonstrated that, furaneol, a known QSI isolated from *Fragaria ananassa* impeded the LasR transcriptional regulators thereby inhibiting the production of elastase in *P. aeruginosa* cultures. Further, they confirmed the effect of the QSI in patients with CF, a dose dependent wound healing response was observed following the application of the candidate QSI.

Another important aspects of QSI affecting the human health involves the possible effect of QSI on the dynamics of microbial community in human gut (McCarthy and O'Gara 2015). It has been well established microbial community in human body produce signalling molecules including AHLs (Yin et al. 2012; Swearingen et al. 2013). Thus inhibitory effect of QSIs on these microbial community is highly probable. However, this possibility and the outcome yet to be studied in human. Dietary phytochemicals exhibiting anti-QS or more specifically signal degrading activity could modulate the signalling system in commensal microbial communities. As these microbial communities are also responsible for host metabolic condition such as diabetes and obesity (Hur and Lee 2015), the shift in microbial profile under the effect of dietary QSI or as therapeutic is likely to be more possible. Thus understanding and gaining deep view of interconnection between QSI and gut microbial flora would clearly enhance our understanding of population dynamics, and their role in development of specific metabolic condition. The influence of dietary substances on microbial signalling within human host may also have medicinal impact (McCarthy and O'Gara 2015). Future work on the determining the interaction between QSI and human microbiome and their possible outcome will open entirely new arena of disease management. The development of pharmaceuticals, nutraceuticals and functional food with their possible role in modulating over all human microbiome will not only substantiate our battle against bacterial infection but also proved to be effective against other pathophysiological conditions.

20.5 Conclusion

Bacterial pathogenicity is a multifactorial phenomenon involving complex process of host-pathogen interaction. The degree of the pathogenicity is controlled through various cell structures and extracellular products called virulence factors. Expression of various virulence factors are known to be regulated through Quorum sensing. It is expected that attenuating virulence through QS interference in pathogenic bacteria may successfully result in disease control especially where antibiotic is ineffective due development of multi drug resistance. The literature survey in this article revealed that several plant derived products and phytocompounds can be considered as promising candidate for anti-infective drug development. However, further evaluation of these compounds using *in vivo* infection model for their proved therapeutic effectiveness are needed. To exploit anti-QS strategy in the control of bacterial infections, what is more challenging is to obtain active compound or formulation effective against number of QS network present in pathogenic bacteria to attenuate its virulence effectively, so that host defence system can clear the infectious agent.

20.6 Opinion

Considering the current global scenario of emergence and spread of MDR pathogens and slow discovery of new antibiotics with novel mode of action, it is necessary to develop alternative mode of bacterial infection control. The progress made so far on the role of QSI in the treatment of bacterial infection still weak and clumsy. Therefore, more concerted efforts should be directed to understand the linkage of various virulence factors with QS and how to effectively target virulence of pathogen through QS inhibition as well as use of other strategy in combination with QSIs.

References

Abraham I, Packiavathy V, Sasikumar P, Pandian SK, Ravi AV (2013) Prevention of quorum-sensing-mediated biofilm development and virulence factors production in *Vibrio* spp. by curcumin. Appl Microbiol Biotechnol 97(23):10177. https://doi.org/10.1007/s00253-013-4704-5

Adonizio AL, Downum K, Bennett BC, Mathee K (2006) Anti-quorum sensing activity of medicinal plants in southern Florida. J Ethnopharmacol 105(3):427–435. https://doi.org/10.1016/j.jep.2005.11.025

Ahmad I, Khan MSA, Husain FM, Zahin M, Singh M (2011) Bacterial quorum sensing and its interference: methods and significance. In: Ahmad I, Ahmad F, Pichtel J (eds) Microbes and microbial technology. Springer, New York, pp 127–161. https://doi.org/10.1007/978-1-4419-7931-5_6

Ahmad A, Viljoen AM, Chenia HY (2015) The impact of plant volatiles on bacterial quorum sensing. Lett Appl Microbiol 60(1):8–19. https://doi.org/10.1111/lam.12343

Al-Shabib NA, Husain FM, Ahmad I, Baig MH (2016) Eugenol inhibits quorum sensing and biofilm of toxigenic MRSA strains isolated from food handlers employed in Saudi Arabia. Biotechnol Biotechnol Equip 31(2):387–396. https://doi.org/10.1080/13102818.2017.1281761

Alves S, Duarte A, Sousa S, Domingues FC (2016) Study of the major essential oil compounds of *Coriandrum sativum* against *Acinetobacter baumannii* and the effect of linalool on adhesion, biofilms and quorum sensing. Biofouling 32(2):155–165. https://doi.org/10.1080/08927014.2015.1133810

Aqil F, Ahmad I, Owais M (2006) Ch. 9: targeted screening of bioactive plant extracts and Phytocompounds against problematic groups of multidrug-resistant bacteria. In: Ahmad I, Aqil F, Owais M (eds) Modern phytomedicine: turning medicinal plants into drugs. Wiley-VCH, Weinheim. https://doi.org/10.1002/9783527609987

Asfour HZ (2017) Anti-quorum sensing natural compounds. J Microsc Ultrastruct. https://doi.org/10.1016/j.jmau.2017.02.001

Asghar A, Butt MS, Shahid M, Huang Q (2017) Evaluating the antimicrobial potential of green cardamom essential oil focusing on quorum sensing inhibition of *Chromobacterium violaceum*. Food Sci Technol 54:2306. https://doi.org/10.1007/s1319

Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, Temml V, Wang L, Schwaiger S, Heiss EH, Rollinger JM (2015) Discovery and resupply of pharmacologically active plant-derived natural products: a review. Biotechnol Adv 33(8):1582–1614. https://doi.org/10.1016/j.biotechadv.2015.08.001

Bai AJ, Vittal RR (2014) Quorum sensing inhibitory and anti-biofilm activity of essential oils and their in vivo efficacy in food systems. Food Biotechnol 28(3):269–292. https://doi.org/10.1080/08905436.2014.932287

Bakkali F, Averbeck S, Averbeck D, Idaomar M (2008) Biological effects of essential oils–a review. Food Chem Toxicol 46(2):446–475. https://doi.org/10.1016/j.fct.2007.09.106

Bezek K, Kurinčič M, Knauder E, Klančnik A, Raspor P, Bucar F, Smole Možina S (2016) Attenuation of adhesion, biofilm formation and quorum sensing of *Campylobacter jejuni* by *Euodia ruticarpa*. Phytother Res 30(9):1527–1532. https://doi.org/10.1002/ptr.5658

Bhargava N, Singh SP, Sharma A, Sharma P, Capalash N (2015) Attenuation of quorum sensing-mediated virulence of *Acinetobacter baumannii* by *Glycyrrhiza glabra* flavonoids. Future Microbiol 10(12):1953–1968. https://doi.org/10.2217/fmb.15.107

Bjarnsholt T, Givskov M (2007) Quorum-sensing blockade as a strategy for enhancing host defences against bacterial pathogens. Philos Trans R Soc Lond Ser B Biol Sci 362(1483):1213–1222. https://doi.org/10.1098/rstb.2007.2046

Borges A, Serra S, Cristina Abreu A, Saavedra MJ, Salgado A, Simões M (2014) Evaluation of the effects of selected phytochemicals on quorum sensing inhibition and in vitro cytotoxicity. Biofouling 30(2):183–195. https://doi.org/10.1080/08927014.2013.852542

Brango-Vanegas J, Costa GM, Ortmann CF, Schenkel EP, Reginatto FH, Ramos FA, Arévalo-Ferro C, Castellanos L (2014) Glycosylflavonoids from Cecropia pachystachya Trécul are quorum sensing inhibitors. Phytomedicine 21(5):670–675. https://doi.org/10.1016/j.phymed.2014.01.001

Camara M, Williams P, Hardman A (2002) Controlling infection by tuning in and turning down the volume of bacterial small-talk. Lancet Infect Dis 2(11):667–676

Castillo S, Heredia N, Arechiga-Carvajal E, García S (2014) Citrus extracts as inhibitors of quorum sensing, biofilm formation and motility of *Campylobacter jejuni*. Food Biotechnol 28(2):106–122. https://doi.org/10.1080/08905436.2014.895947

Cegelski L, Marshall GR, Eldridge GR, Hultgren SJ (2008) The biology and future prospects of antivirulence therapies. Nat Rev Microbiol 6(1):17. https://doi.org/10.1038/nrmicro1818

Cervantes-Ceballos L, Caballero-Gallardo K, Olivero-Verbel J (2015) Repellent and anti-quorum sensing activity of six aromatic plants occurring in Colombia. Nat Prod Commun 10(10):1753–1757

Ceylan O, Sahin MD, Akdamar G (2016) Antioxidant and anti-quorum sensing potential of *Acer monspessulanum* subsp. *monspessulanum* extracts. Planta Med 82(15):1335–1340. https://doi.org/10.1055/s-0042-105294

Chen Y, Liu T, Wang K, Hou C, Cai S, Huang Y, Du Z, Huang H, Kong J, Chen Y (2016) Baicalein inhibits *Staphylococcus aureus* biofilm formation and the quorum sensing system in vitro. PLoS One 11(4):e0153468. https://doi.org/10.1371/journal.pone.0153468

Chenia HY (2013) Anti-quorum sensing potential of crude *Kigelia africana* fruit extracts. Sensors (Basel) 13(3):2802–2817. https://doi.org/10.3390/s130302802

Chong YM, Yin WF, Ho CY, Mustafa MR, Hadi AH, Awang K, Narrima P, Koh CL, Appleton DR, Chan KG (2011) Malabaricone C from *Myristica cinnamomea* exhibits anti-quorum sensing activity. J Nat Prod 74(10):2261–2264. https://doi.org/10.1021/np100872k

Christensen LD, Moser C, Jensen PØ, Rasmussen TB, Christophersen L, Kjelleberg S, Kumar N, Høiby N, Givskov M, Bjarnsholt T (2007) Impact of *Pseudomonas aeruginosa* quorum sensing on biofilm persistence in an in vivo intraperitoneal foreign-body infection model. Microbiology 153(Pt 7):2312–2320. https://doi.org/10.1099/mic.0.2007/006122-0

Chu W, Zhou S, Jiang Y, Zhu W, Zhuang X, Fu J (2013) Effect of traditional Chinese herbal medicine with antiquorum sensing activity on *Pseudomonas aeruginosa*. Evid Based Complement Alternat Med 2013:648257. https://doi.org/10.1155/2013/648257

Cosa S, Viljoen AM, Chaudhary SK, Chen W (2016) Hacking in to the social media network of bacteria: the antiquorum sensing properties of herbs and spices. Planta Med 82(S01):S1–S381. https://doi.org/10.1055/s-0036-1596316

Cowan MM (1999) Plant products as antimicrobial agents. Clin Microbiol Rev 12(4):564–582

Duarte A, Luís Â, Oleastro M, Domingues FC (2016) Antioxidant properties of coriander essential oil and linalool and their potential to control *Campylobacter* spp. Food Control 61:115–122. https://doi.org/10.1016/j.foodcont.2015.09.033

Elmanama AA, Al-Reefi MR (2017) Antimicrobial, anti-biofilm, anti-quorum sensing, antifungal and synergistic effects of some medicinal plants extracts. IUG J Nat Stud 25(2):198–207

Eris R, Ulusoy S (2013) Rose, clove, chamomile essential oils and pine turpentine inhibit quorum sensing in *Chromobacterium violaceum* and *Pseudomonas aeruginosa*. J Essent Oil Bear Plants 16(2):126–135. https://doi.org/10.1080/0972060X.2013.794026

Fatima Q, Zahin M, Khan MS, Ahmad I (2010) Modulation of quorum sensing controlled behaviour of bacteria by growing seedling, seed and seedling extracts of leguminous plants. Indian J Microbiol 50(2):238–242. https://doi.org/10.1007/s12088-010-0025-x

Fratianni F, Coppola R, Nazzaro F (2011) Phenolic composition and antimicrobial and antiquorum sensing activity of an ethanolic extract of peels from the apple cultivar Annurca. J Med Food 14(9):957–963. https://doi.org/10.1089/jmf.2010.0170

Ganesh PS, Rai VR (2015) Evaluation of anti-bacterial and anti-quorum sensing potential of essential oils extracted by supercritical CO_2 method against *Pseudomonas aeruginosa*. J Essent Oil Bear Plants 18(2):264–275. https://doi.org/10.1080/0972060X.2015.1025295

Ganesh PS, Rai RV (2016) Inhibition of quorum-sensing-controlled virulence factors of *Pseudomonas aeruginosa* by *Murraya koenigii* essential oil: a study in a *Caenorhabditis elegans* infectious model. J Med Microbiol 65(12):1528–1535. https://doi.org/10.1099/jmm.0.000385

Ganesh PS, Rai VR (2017) Attenuation of quorum-sensing-dependent virulence factors and biofilm formation by medicinal plants against antibiotic resistant *Pseudomonas aeruginosa*. J Tradit Complement Med. https://doi.org/10.1016/j.jtcme.2017.05.008

Ghosh R, Tiwary BK, Kumar A, Chakraborty R (2014) Guava leaf extract inhibits quorum-sensing and *Chromobacterium violaceum* induced lysis of human hepatoma cells: whole transcriptome analysis reveals differential gene expression. PLoS One 9(9):e107703. https://doi.org/10.1371/journal.pone.0107703

Gökalsın B, Aksoydan B, Erman B, Sesal NC (2017) Reducing virulence and biofilm of *Pseudomonas aeruginosa* by potential quorum sensing inhibitor carotenoid: zeaxanthin. Microb Ecol 74(2):466–473. https://doi.org/10.1007/s00248-017-0949-3

Gopu V, Kothandapani S, Shetty PH (2015a) Quorum quenching activity of *Syzygium cumini* (L.) Skeels and its anthocyanin malvidin against *Klebsiella pneumoniae*. Microb Pathog 79:61–69. https://doi.org/10.1016/j.micpath.2015.01.010

Gopu V, Meena CK, Shetty PH (2015b) Quercetin influences quorum sensing in food borne bacteria: in-vitro and in-silico evidence. PLoS One 10(8):e0134684. https://doi.org/10.1371/journal.pone.0134684

Gopu V, Meena CK, Murali A, Shetty PH (2016) Petunidin as a competitive inhibitor of acylated homoserine lactones in *Klebsiella pneumoniae*. RSC Adv 6(4):2592–2601. https://doi.org/10.1039/C5RA20677D

Gutiérrez-Barranquero JA, Reen FJ, McCarthy RR, O'Gara F (2015) Deciphering the role of coumarin as a novel quorum sensing inhibitor suppressing virulence phenotypes in bacterial pathogens. Appl Microbiol Biotechnol 99(7):3303–3316. https://doi.org/10.1007/s00253-015-6465-9

Harjai K, Kumar R, Singh S (2010) Garlic blocks quorum sensing and attenuates the virulence of *Pseudomonas aeruginosa*. FEMS Immunol Med Microbiol 58(2):161–168. https://doi.org/10.1111/j.1574-695X.2009.00614.x

Hossain MA, Lee SJ, Park JY, Reza MA, Kim TH, Lee KJ, Suh JW, Park SC (2015) Modulation of quorum sensing-controlled virulence factors by *Nymphaea tetragona* (water lily) extract. J Ethnopharmacol 174:482–491. https://doi.org/10.1016/j.jep.2015.08.049

Hur KY, Lee MS (2015) Gut microbiota and metabolic disorders. Diabetes Metab J 39(3):198–203. https://doi.org/10.4093/dmj.2015.39.3.198

Husain FM, Ahmad I (2013) Quorum sensing inhibitors from natural products as potential novel anti-infective agents. Drugs Future 38(10):691. https://doi.org/10.1358/dof.2013.038.10.2025393

Husain FM, Ahmad I, Asif M, Tahseen Q (2013) Influence of clove oil on certain quorum-sensing-regulated functions and biofilm of *Pseudomonas aeruginosa* and *Aeromonas hydrophila*. J Biosci 38(5):835–844

Husain FM, Ahmad I, Khan MS, Al-Shabib NA (2015a) *Trigonella foenum-graceum* (seed) extract interferes with quorum sensing regulated traits and biofilm formation in the strains of *Pseudomonas aeruginosa* and *Aeromonas hydrophila*. Evid Based Complement Alternat Med 2015:879540. https://doi.org/10.1155/2015/879540

Husain FM, Ahmad I, Khan MS, Ahmad E, Tahseen Q, Khan MS, Alshabib NA (2015b) Sub-MICs of *Mentha piperita* essential oil and menthol inhibits AHL mediated quorum sensing and biofilm of Gram-negative bacteria. Front Microbiol 6:420. https://doi.org/10.3389/fmicb.2015.00420

Husain FM, Ahmad I, Al-thubiani AS, Abulreesh HH, AlHazza IM, Aqil F (2017) Leaf extracts of *Mangifera indica* l. inhibit quorum sensing–regulated production of virulence factors and biofilm in test bacteria. Front Microbiol 8:727. https://doi.org/10.3389/fmicb.2017.00727

Ilic-Tomic T, Sokovic M, Vojnovic S, Ciric A, Veljic M, Nikodinovic-Runic J, Novakovic M (2017) Diarylheptanoids from *Alnus viridis* ssp. *viridis* and *Alnus glutinosa*: modulation of quorum sensing activity in *Pseudomonas aeruginosa*. Planta Med 83(01/02):117–125. https://doi.org/10.1055/s-0042-107674

Kalia VC (2013) Quorum sensing inhibitors: an overview. Biotechnol Adv 31(2):224–245. https://doi.org/10.1016/j.biotechadv.2012.10.004

Kalia M, Yadav VK, Singh PK, Sharma D, Pandey H, Narvi SS, Agarwal V (2015) Effect of cinnamon oil on quorum sensing-controlled virulence factors and biofilm formation in *Pseudomonas aeruginosa*. PLoS One 10(8):e0135495. https://doi.org/10.1371/journal.pone.0135495

Khan MS, Zahin M, Hasan S, Husain FM, Ahmad I (2009) Inhibition of quorum sensing regulated bacterial functions by plant essential oils with special reference to clove oil. Lett Appl Microbiol 49(3):354–360. https://doi.org/10.1111/j.1472-765X.2009.02666.x

Kim HS, Lee SH, Byun Y, Park HD (2015) 6-Gingerol reduces *Pseudomonas aeruginosa* biofilm formation and virulence via quorum sensing inhibition. Sci Rep 5. https://doi.org/10.1038/srep08656

Koh KH, Tham FY (2011) Screening of traditional Chinese medicinal plants for quorum-sensing inhibitors activity. J Microbiol Immunol Infect 44(2):144–148. https://doi.org/10.1016/j.jmii.2009.10.001

Koh CL, Sam CK, Yin WF, Tan LY, Krishnan T, Chong YM, Chan KG (2013) Plant-derived natural products as sources of anti-quorum sensing compounds. Sensors 13(5):6217–6228. https://doi.org/10.3390/s130506217

Kordbacheh H, Eftekhar F, Ebrahimi SN (2017) Anti-quorum sensing activity of *Pistacia atlantica* against *Pseudomonas aeruginosa* PAO1 and identification of its bioactive compounds. Microb Pathog 110:390–398. https://doi.org/10.1016/j.micpath.2017.07.018

Kothari V, Patel P, Joshi C (2017) Bioactive natural products: an overview, with particular emphasis on those possessing potential to inhibit microbial quorum sensing. In: Kalia VC (ed) Microbial applications, vol 2. Springer, Cham, pp 185–202. https://doi.org/10.1007/978-3-319-52669-0_10

Kumar S, Pandey AK (2013) Chemistry and biological activities of flavonoids: an overview. Scientific World J 2013:162750. https://doi.org/10.1155/2013/162750

Kumar L, Chhibber S, Kumar R, Kumar M, Harjai K (2015) Zingerone silences quorum sensing and attenuates virulence of *Pseudomonas aeruginosa*. Fitoterapia 102:84–95. https://doi.org/10.1016/j.fitote.2015.02.002

LaSarre B, Federle MJ (2013) Exploiting quorum sensing to confuse bacterial pathogens. Microbiol Mol Biol Rev 77(1):73–111. https://doi.org/10.1128/MMBR.00046-12

Lazdunski AM, Ventre I, Sturgis JN (2004) Regulatory circuits and communication in Gram-negative bacteria. Nature Rev Microbiol 2:581–592. https://doi.org/10.1038/nrmicro924

Li G, Yan C, Xu Y, Feng Y, Wu Q, Lv X, Yang B, Wang X, Xia X (2014) Punicalagin inhibits Salmonella virulence factors and has anti-quorum-sensing potential. Appl Environ Microbiol 80(19):6204–6211. https://doi.org/10.1128/AEM.01458-14

Luciardi MC, Blázquez MA, Cartagena E, Bardón A, Arena ME (2016) Mandarin essential oils inhibit quorum sensing and virulence factors of *Pseudomonas aeruginosa*. LWT Food Sci Technol 68:373–380. https://doi.org/10.1016/j.lwt.2015.12.056

Luis Â, Duarte A, Gominho J, Domingues F, Duarte AP (2016) Chemical composition, antioxidant, antibacterial and anti-quorum sensing activities of *Eucalyptus globulus* and *Eucalyptus radiata* essential oils. Ind Crop Prod 79:274–282. https://doi.org/10.1016/j.indcrop.2015.10.055

Luo J, Dong B, Wang K, Cai S, Liu T, Cheng X, Lei D, Chen Y, Li Y, Kong J, Chen Y (2017) Baicalin inhibits biofilm formation, attenuates the quorum sensing-controlled virulence and enhances *Pseudomonas aeruginosa* clearance in a mouse peritoneal implant infection model. PLoS One 12(4):e0176883. https://doi.org/10.1371/journal.pone.0176883

Maisuria VB, Lopez-de Los Santos Y, Tufenkji N, Déziel E (2016) Cranberry-derived proanthocyanidins impair virulence and inhibit quorum sensing of *Pseudomonas aeruginosa*. Sci Rep 6:30169. https://doi.org/10.1038/srep30169

Majik MS, Naik D, Bhat C, Tilve S, Tilvi S, D'Souza L (2013) Synthesis of (R)-norbgugaine and its potential as quorum sensing inhibitor against *Pseudomonas aeruginosa*. Bioorg Med Chem Lett 23(8):2353–2356. https://doi.org/10.1016/j.bmcl.2013.02.051

Makhfian M, Hassanzadeh N, Mahmoudi E, Zandyavari N (2015) Anti-quorum sensing effetcs of ethanolic crude extract of *Anethum graveolens* L. J Essent Oil Bear Plants 18(3):687–696. https://doi.org/10.1080/0972060X.2014.998718

Martín-Rodríguez AJ, Ticona JC, Jiménez IA, Flores N, Fernández JJ, Bazzocchi IL (2015) Flavonoids from *Piper delineatum* modulate quorum-sensing-regulated phenotypes in *Vibrio harveyi*. Phytochemistry 117:98–106. https://doi.org/10.1016/j.phytochem.2015.06.006

McCarthy RR, O'Gara F (2015) The impact of phytochemicals present in the diet on microbial signalling in the human gut. J Funct Foods 14:684–691. https://doi.org/10.1016/j.jff.2015.02.032

Miller MB, Bassler BL (2001) Quorum sensing in bacteria. Annu Rev Microbiol 55(1):165–199. https://doi.org/10.1146/annurev.micro.55.1.165

Muhs A, Lyles JT, Parlet CP, Nelson K, Kavanaugh JS, Horswill AR, Quave CL (2017) Virulence inhibitors from brazilian peppertree block quorum sensing and abate dermonecrosis in skin infection models. Sci Rep 7:42275. https://doi.org/10.1038/srep42275

Musthafa KS, Ravi AV, Annapoorani A, Packiavathy IS, Pandian SK (2010) Evaluation of anti-quorum-sensing activity of edible plants and fruits through inhibition of the N-acyl-homoserine lactone system in *Chromobacterium violaceum* and *Pseudomonas aeruginosa*. Chemotherapy 56(4):333–339. https://doi.org/10.1159/000320185

Musthafa KS, Sianglum W, Saising J, Lethongkam S, Voravuthikunchai SP (2017) Evaluation of phytochemicals from medicinal plants of Myrtaceae family on virulence factor production by *Pseudomonas aeruginosa*. APMIS 125(5):482–490. https://doi.org/10.1111/apm.12672

Myszka K, Schmidt MT, Majcher M, Juzwa W, Olkowicz M, Czaczyk K (2016) Inhibition of quorum sensing-related biofilm of *Pseudomonas fluorescens* KM121 by *Thymus vulgare* essential oil and its major bioactive compounds. Int Biodeter Biodegr 114:252–259. https://doi.org/10.1016/j.ibiod.2016.07.006

Nazzaro F, Fratianni F, Coppola R (2013) Quorum sensing and phytochemicals. Int J Mol Sci 14(6):12607–12619. https://doi.org/10.3390/ijms140612607

Nidadavolu P, Amor W, Tran PL, Dertien J, Colmer-Hamood JA, Hamood AN (2012) Garlic ointment inhibits biofilm formation by bacterial pathogens from burn wounds. J Med Microbiol 61(Pt 5):662–671. https://doi.org/10.1099/jmm.0.038638-0

Noumi E, Snoussi M, Merghni A, Nazzaro F, Quindós G, Akdamar G, Mastouri M, Al-Sieni A, Ceylan O (2017) Phytochemical composition, anti-biofilm and anti-quorum sensing potential of fruit, stem and leaves of *Salvadora persica* L. methanolic extracts. Microb Pathog 109:169–176. https://doi.org/10.1016/j.micpath.2017.05.036

Oliveira BD, Rodrigues AC, Cardoso BM, Ramos AL, Bertoldi MC, Taylor JG, da Cunha LR, Pinto UM (2016) Antioxidant, antimicrobial and anti-quorum sensing activities of *Rubus rosaefolius* phenolic extract. Ind Crop Prod 84:59–66. https://doi.org/10.1016/j.indcrop.2016.01.037

Olivero-Verbel J, Barreto-Maya A, Bertel-Sevilla A, Stashenko EE (2014) Composition, anti-quorum sensing and antimicrobial activity of essential oils from *Lippia alba*. Braz J Microbiol 45(3):59–767

Ouedraogo V, Kiendrebeogo M (2016) Methanol extract from *Anogeissus leiocarpus* (DC) Guill. Et Perr.(Combretaceae) stem bark quenches the quorum sensing of *Pseudomonas aeruginosa* PAO1. Medicines (Basel) 3:26. https://doi.org/10.3390/medicines3040026

Packiavathy IA, Agilandeswari P, Musthafa KS, Pandian SK, Ravi AV (2012) Antibiofilm and quorum sensing inhibitory potential of *Cuminum cyminum* and its secondary metabolite methyl eugenol against Gram negative bacterial pathogens. Food Res Int 45(1):85–92. https://doi.org/10.1016/j.foodres.2011.10.022

Packiavathy IA, Priya S, Pandian SK, Ravi AV (2014) Inhibition of biofilm development of uropathogens by curcumin–an anti-quorum sensing agent from *Curcuma longa*. Food Chem 148:453–460. https://doi.org/10.1016/j.foodchem.2012.08.002

Paczkowski JE, Mukherjee S, McCready AR, Cong JP, Aquino CJ, Kim H, Henke BR, Smith CD, Bassler BL (2017) Flavonoids suppress *Pseudomonas aeruginosa* virulence through allosteric inhibition of quorum-sensing receptors. J Biol Chem 292(10):4064–4076. https://doi.org/10.1074/jbc.M116.770552

Palombo EA (2011) Traditional medicinal plant extracts and natural products with activity against oral bacteria: potential application in the prevention and treatment of oral diseases. Evid Based Complement Alternat Med 2011:680354. https://doi.org/10.1093/ecam/nep067

Papaioannou E, Utari PD, Quax WJ (2013) Choosing an appropriate infection model to study quorum sensing inhibition in Pseudomonas infections. Int J Mol Sci 14(9):19309–19340. https://doi.org/10.3390/ijms140919309

Patel B, Kumari S, Banerjee R, Samanta M, Das S (2017) Disruption of the quorum sensing regulated pathogenic traits of the biofilm-forming fish pathogen *Aeromonas hydrophila* by tannic acid, a potent quorum quencher. Biofouling 33(7):580–590. https://doi.org/10.1080/08927014.2017.1336619

Pellegrini MC, Alvarez MV, Ponce AG, Cugnata NM, De Piano FG, Fuselli SR (2014) Anti-quorum sensing and antimicrobial activity of aromatic species from South America. J Essent Oil Res 26(6):458–465. https://doi.org/10.1080/10412905.2014.947387

Pratiwi SU, Hertiani T, Idroes R, Lagendijk EL, de Weert S, Hondel CV (2016) Quorum quenching and biofilm-degrading activity of massoia oil against *Candida albicans* and *Pseudomonas aeruginosa*. Planta Med 81(S01):S1–S381. https://doi.org/10.1055/s-0036-1596813

Priha O, Virkajärvi V, Juvonen R, Puupponen-Pimiä R, Nohynek L, Alakurtti S, Pirttimaa M, Storgards E (2014) Quorum sensing signalling and biofilm formation of brewery-derived bacteria, and inhibition of signalling by natural compounds. Curr Microbiol 69(5):617–627. https://doi.org/10.1007/s00284-014-0627-3

Rahman MR, Lou Z, Yu F, Wang P, Wang H (2017) Anti-quorum sensing and anti-biofilm activity of Amomum tsaoko (Amommum tsao-ko Crevost et Lemarie) on foodborne pathogens. Saudi J Biol Sci 24(2):324–330. https://doi.org/10.1016/j.sjbs.2015.09.034

Rama Devi K, Srinivasan R, Kannappan A, Santhakumari S, Bhuvaneswari M, Rajasekar P, Prabhu NM, Veera Ravi A (2016) In vitro and in vivo efficacy of rosmarinic acid on quorum sensing mediated biofilm formation and virulence factor production in *Aeromonas hydrophila*. Biofouling 32(10):1171–1183. https://doi.org/10.1080/08927014.2016.1237220

Rasamiravaka T, Jedrzejowski A, Kiendrebeogo M, Rajaonson S, Randriamampionona D, Rabemanantsoa C, Andriantsimahavandy A, Rasamindrakotroka A, Duez P, El Jaziri M, Vandeputte OM (2013) Endemic Malagasy Dalbergia species inhibit quorum sensing in *Pseudomonas aeruginosa* PAO1. Microbiology 159(Pt 5):924–938. https://doi.org/10.1099/mic.0.064378-0

Rasmussen TB, Givskov M (2006) Quorum sensing inhibitors: a bargain of effects. Microbiology 152(4):895–904. https://doi.org/10.1099/mic.0.28601-0

Rekha PD, Vasavi HS, Vipin C, Saptami K, Arun AB (2017) A medicinal herb Cassia alata attenuates quorum sensing in *Chromobacterium violaceum* and *Pseudomonas aeruginosa*. Lett Appl Microbiol 64(3):231–238. https://doi.org/10.1111/lam.12710

Rodrigues AC, Oliveira BD, Silva ER, Sacramento NT, Bertoldi MC, Pinto UM (2016a) Anti-quorum sensing activity of phenolic extract from *Eugenia brasiliensis* (Brazilian cherry). Food Sci Technol (Campinas) 36(2):337–343. https://doi.org/10.1590/1678-457X.0089

Rodrigues AC, Zola FG, Ávila Oliveira BD, Sacramento NT, da Silva ER, Bertoldi MC, Taylor JG, Pinto UM (2016b) Quorum quenching and microbial control through phenolic extract of *Eugenia uniflora* fruits. J Food Sci 81(10):M2538–M2544. https://doi.org/10.1111/1750-3841.13431

Ruffin M, Bilodeau C, Maillé É, LaFayette SL, McKay GA, Trinh NT, Beaudoin T, Desrosiers MY, Rousseau S, Nguyen D, Brochiero E (2016) Quorum-sensing inhibition abrogates the deleterious impact of *Pseudomonas aeruginosa* on airway epithelial repair. FASEB J 30(9):3011–3025. https://doi.org/10.1096/fj.201500166R

Rumbaugh KP, Griswold JA, Iglewski BH, Hamood AN, Barbara H (1999) Contribution of quorum sensing to the virulence of *Pseudomonas aeruginosa* in burn wound infections. Infect Immun 67(11):5854–5862

Salini R, Sindhulakshmi M, Poongothai T, Pandian SK (2015) Inhibition of quorum sensing mediated biofilm development and virulence in uropathogens by *Hyptis suaveolens*. Antonie Van Leeuwenhoek 107(4):1095–1106. https://doi.org/10.1007/s10482-015-0402-x

Sameena H (2006) Quorum sensing inhibition and antimicrobial properties of certain medicinal plants and natural products. MSc Dissertation (Ag. Microbiology). Submitted to Aligarh Muslim University, Aligarh, India

Sarabhai S, Sharma P, Capalash N (2013) Ellagic acid derivatives from *Terminalia chebula* Retz. Downregulate the expression of quorum sensing genes to attenuate *Pseudomonas aeruginosa* PAO1 virulence. PLoS One 8(1):53441. https://doi.org/10.1371/journal.pone.0053441

Sepahi E, Tarighi S, Ahmadi FS, Bagheri A (2015) Inhibition of quorum sensing in *Pseudomonas aeruginosa* by two herbal essential oils from Apiaceae family. J Microbiol 53(2):176. https://doi.org/10.1007/s12275-015-4203-8

Sethupathy S, Nithya C, Pandian SK (2015) 2-Furaldehyde diethyl acetal from tender coconut water (*Cocos nucifera*) attenuates biofilm formation and quorum sensing-mediated virulence of *Chromobacterium violaceum* and *Pseudomonas aeruginosa*. Biofouling 31(9–10):721–733. https://doi.org/10.1080/08927014.2015.1102897

Sheng JY, Chen TT, Tan XJ, Chen T, Jia AQ (2015) The quorum-sensing inhibiting effects of stilbenoids and their potential structure–activity relationship. Bioorg Med Chem Lett 25(22):5217–5220. https://doi.org/10.1016/j.bmcl.2015.09.064

Silva LN, Zimmer KR, Macedo AJ, Trentin DS (2016) Plant natural products targeting bacterial virulence factors. Chem Rev 116(16):9162–9236. https://doi.org/10.1021/acs.chemrev.6b00184

Singh BN, Upreti DK, Singh BR, Pandey G, Verma S, Roy S, Naqvi AH, Rawat AK (2015) Quercetin sensitizes fluconazole-resistant *Candida albicans* to induce apoptotic cell death by modulating quorum sensing. Antimicrob Agents Chemother 59(4):2153–2168. https://doi.org/10.1128/AAC.03599-14

Srinivasan R, Devi KR, Kannappan A, Pandian SK, Ravi AV (2016) *Piper betle* and its bioactive metabolite phytol mitigates quorum sensing mediated virulence factors and biofilm of nosocomial pathogen *Serratia marcescens* in vitro. J Ethnopharmacol 193:592–603. https://doi.org/10.1016/j.jep.2016.10.017

Srinivasan R, Santhakumari S, Ravi AV (2017) In vitro antibiofilm efficacy of *Piper betle* against quorum sensing mediated biofilm formation of luminescent *Vibrio harveyi*. Microb Pathog 110:232–239. https://doi.org/10.1016/j.micpath.2017.07.001

Sun S, Li H, Zhou W, Liu A, Zhu H (2014) Bacterial quorum sensing inhibition activity of the traditional Chinese herbs, *Ficus carica* L. and *Perilla frutescens*. Chemotherapy 60(5–6):379–383. https://doi.org/10.1159/000440946

Swearingen MC, Sabag-Daigle A, Ahmer BM (2013) Are there acyl-homoserine lactones within mammalian intestines? J Bacteriol 195(2):173–179. https://doi.org/10.1128/JB.01341-12

Szabó MÁ, Varga GZ, Hohmann J, Schelz Z, Szegedi E, Amaral L, Molnár J (2010) Inhibition of quorum-sensing signals by essential oils. Phytother Res 24(5):782–786. https://doi.org/10.1002/ptr.3010

Tapia-Rodriguez MR, Hernandez-Mendoza A, Gonzalez-Aguilar GA, Martinez-Tellez MA, Martins CM, Ayala-Zavala JF (2017) Carvacrol as potential quorum sensing inhibitor of *Pseudomonas aeruginosa* and biofilm production on stainless steel surfaces. Food Control 75:255–261. https://doi.org/10.1016/j.foodcont.2016.12.014

Thakur P, Chawla R, Tanwar A, Chakotiya AS, Narula A, Goel R, Arora R, Sharma RK (2016) Attenuation of adhesion, quorum sensing and biofilm mediated virulence of carbapenem resistant *Escherichia coli* by selected natural plant products. Microb Pathog 92:76–85. https://doi.org/10.1016/j.micpath.2016.01.001

Tiwary BK, Ghosh R, Moktan S, Ranjan VK, Dey P, Choudhury D, Dutta S, Deb D, Das AP, Chakraborty R (2017) Prospective bacterial quorum sensing inhibitors from Indian medicinal plant extracts. Lett Appl Microbiol 65(1):2–10. https://doi.org/10.1111/lam.12748

Truchado P, Giménez-Bastida JA, Larrosa M, Castro-Ibáñez I, Espín JC, Tomás-Barberán FA, García-Conesa MT, Allende A (2012) Inhibition of quorum sensing (QS) in *Yersinia enterocolitica* by an orange extract rich in glycosylated flavanones. J Agric Food Chem 60(36):8885–8894. https://doi.org/10.1021/jf301365a

Truchado P, Larrosa M, Castro-Ibáñez I, Allende A (2015) Plant food extracts and phytochemicals: their role as quorum sensing inhibitors. Trends Food Sci Technol 43(2):189–204. https://doi.org/10.1016/j.tifs.2015.02.009

Vandeputte OM, Kiendrebeogo M, Rajaonson S, Diallo B, Mol A, El Jaziri M, Baucher M (2010) Identification of catechin as one of the flavonoids from *Combretum albiflorum* bark extract that reduces the production of quorum-sensing-controlled virulence factors in *Pseudomonas aeruginosa* PAO1. Appl Environ Microbiol 76(1):243–253. https://doi.org/10.1128/AEM.01059-09

Vandeputte OM, Kiendrebeogo M, Rasamiravaka T, Stevigny C, Duez P, Rajaonson S, Diallo B, Mol A, Baucher M, El Jaziri M (2011) The flavanone naringenin reduces the production of quorum sensing-controlled virulence factors in *Pseudomonas aeruginosa* PAO1. Microbiology 157(7):2120–2132. https://doi.org/10.1099/mic.0.049338-0

Vasavi HS, Arun AB, Rekha PD (2014) Anti-quorum sensing activity of *Psidium guajava* L. flavonoids against *Chromobacterium violaceum* and *Pseudomonas aeruginosa* PAO1. Microbiol Immunol 58(5):286–293. https://doi.org/10.1111/1348-0421.12150

Vasavi HS, Arun AB, Rekha PD (2015) Anti-quorum sensing potential of *Adenanthera pavonina*. Pharm Res 7(1):105–109. https://doi.org/10.4103/0974-8490.147220

Vattem DA, Mihalik K, Crixell SH, McLean RJ (2007) Dietary phytochemicals as quorum sensing inhibitors. Fitoterapia 78(4):302–310. https://doi.org/10.1016/j.fitote.2007.03.009

Yang Q, Wang L, Gao J, Liu X, Feng Y, Wu Q, Baloch AB, Cui L, Xia X (2016) Tannin-rich fraction from pomegranate rind inhibits quorum sensing in *Chromobacterium violaceum* and biofilm formation in *Escherichia coli*. Foodborne Pathog Dis 13(1):28–35. https://doi.org/10.1089/fpd.2015.2027

Yap PS, Krishnan T, Yiap BC, Hu CP, Chan KG, Lim SH (2014) Membrane disruption and anti-quorum sensing effects of synergistic interaction between Lavandula angustifolia (lavender oil) in combination with antibiotic against plasmid-conferred multi-drug-resistant Escherichia coli. J Appl Microbiol 116(5):1119–1128. https://doi.org/10.1111/jam.12444

Yarmolinsky L, Bronstein M, Gorelick J (2015) Inhibition of bacterial quorum sensing by plant extracts. Isr J Plant Sci 62(4):294–297. https://doi.org/10.1080/07929978.2015.1067076

Yin WF, Purmal K, Chin S, Chan XY, Chan KG (2012) Long chain N-acyl homoserine lactone production by Enterobacter sp. isolated from human tongue surfaces. Sensors 12(11):14307–14314. https://doi.org/10.3390/s121114307

Yin H, Deng Y, Wang H, Liu W, Zhuang X, Chu W (2015) Tea polyphenols as an antivirulence compound disrupt quorum-sensing regulated pathogenicity of *Pseudomonas aeruginosa*. Sci Rep 6:17987. https://doi.org/10.1038/srep17987

Zahin M, Aqil F, Khan MS, Ahmad I (2010a) Ethnomedicinal plants derived antibacterials and their prospects. In: Chattopadhyay D (ed) Ethnomedicine: a source of complementary therapeutics. Research Signpost, Trivandrum, pp 149–178

Zahin M, Hasan S, Aqil F, Khan M, Ahmad S, Husain FM, Ahmad I (2010b) Screening of certain medicinal plants from India for their anti-quorum sensing activity. Indian J Exp Biol 48(12):1219–1224

Zhang A, Chu WH (2017) Anti-quorum sensing activity of Forsythia suspense on *Chromobacterium violaceum* and *Pseudomonas aeruginosa*. Pharmacogn Mag 13(50):321–325. https://doi.org/10.4103/0973-1296.204547

Zhou L, Zheng H, Tang Y, Yu W, Gong Q (2013) Eugenol inhibits quorum sensing at sub-inhibitory concentrations. Biotechnol Lett 35(4). https://doi.org/10.1007/s10529-012-1126-x

Zhu J, Huang X, Zhang F, Feng L, Li J (2015) Inhibition of quorum sensing, biofilm, and spoilage potential in *Shewanella baltica* by green tea polyphenols. J Microbiol 53(12):829–836. https://doi.org/10.1007/s12275-015-5123-3