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MEDICINAL PLANTS AND PHYTOCHEMICALS AGAINST *PSEUDOMONAS AERUGINOSA* QUORUM SENSING

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ABSTRACT: Medicinal plants are significantly used in the cure of various ailments from ancient times. Literature suggests that traditional medicinal plants from Fabaceae, Lamiaceae, Myrtaceae, and Anacardiaceae, Combretaceae family are widely studied, and they potentially inhibit quorum sensing, a bacterial communication mechanism that leads to the pathogenesis. Plants such as *Anogeissus leiocarpus*, *Brassia oleraceae*, *Camellia nitidissima*, *Cassia alata*, *Laserpitium ochridanum*, *Neppenthes alata*, *Parkia javanica*, *Pistacia atlantica*, *Plantago asiatica*, *Psidium guajava*, *Quercus infectoria*, *Terminallia bellerica*, *Terminallia catappa*, are reported to be effective in quorum sensing inhibition. Plant extracts containing phytochemicals such as quercetin, kaempferol, myricetin, baicalin, cassipourol, 6-gingerol and eugenol were reported to be potential inhibitors of *Pseudomonas aeruginosa* quorum sensing. Bioactive principles from medicinal plants with anti-quorum sensing properties are remarkable substitutes for synthetic antibacterial drugs, especially in the era of multi-drug resistant (MDR) pathogens. The anti-quorum sensing activity of medicinal plants against the *Pseudomonas aeruginosa*, a gram-negative MDR bacterium, is reviewed for the period from 1997 to 2019.

INTRODUCTION: Quorum sensing (QS) is a cell-to-cell communication process in bacteria to stimulate and respond based on population density through small signaling molecules [1]. Bacteria use QS systems to coordinate certain behaviors such as biofilm formation, virulence, and antibiotic production. Recently, quorum sensing has been shown to be involved in the development of resistance to various antimicrobial treatments and immune modulation.

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A drug that is capable of blocking QS is likely to increase the susceptibility of the infecting organism to host defenses and its clearance from the host. Since pathogenicity in many bacteria is regulated by QS, inhibition of this mechanism may lead to the suppression of virulence [2].

The use of quorum sensing inhibitors (QSI) to attenuate bacterial pathogenicity, is highly attractive, particularly with respect to the emergence of the multi-antibiotic resistant bacteria *P. aeruginosa*. Interference with quorum sensing could be a novel approach to control bacterial infections as many bacteria rely on quorum sensing [3]. The World Health Organization (WHO) reported that 80% of the world's population use herbal medicines for their primary healthcare [4]. Natural products play a vital role in treating and preventing infectious diseases, and many approved drugs that we are using nowadays are derived from medicinal plants. To date, several studies have been focused on herbs that play a major role in the prevention, management, and treatment of various diseases due to their efficacy, less side effects, and relatively cost-effectiveness [5]. Contribution of medicinal plants towards ayurvedic medicine increased the potentiality of plant-derived novel drugs that enhance human health *via* their medicinal properties [6]. Here, we present an up-to-date review on medicinal plants with potential quorum sensing inhibitory effect with special emphasis on plant family, extraction methods, solvents used, and efficacy.

Multi-Drug Resistance: According to WHO, resistant microorganisms such as bacteria, fungi, viruses, and parasites can combat antimicrobial drugs, which leads to ineffective treatment resulting in the persistence of infections. Although the development of multidrug resistance is a natural phenomenon, its huge rise in recent years has become a major threat to mankind, especially among the immunocompromised individuals [7]. The process of drug discovery of new antimicrobial drugs takes a long time.

Hence, only very few new agents have recently been approved by the FDA and are available for use. The Infectious Diseases Society of America (IDSA) recognizes anti-microbial resistance as "one of the greatest threats to human health worldwide" [8]. Hence, the identification and evaluation of new antimicrobials with alternate strategy is much warranted.

***Pseudomonas aeruginosa* – A superbug:** *Pseudomonas aeruginosa* is a life-threatening gram-negative bacterium in immunocompromised patients. It is a common cause of pneumonia, urinary tract and surgical-site infections, burn infections, and plays a vital role in cystic fibrosis infections. It can even lead to lethal conditions, especially due to its intrinsic resistance to antibiotics [9]. It is one of the uropathogens that resist the action of several antibiotics due to biofilm formation [10]. A range of mechanisms for adaptation, survival, and resistance against multiple classes of antibiotics makes *P. aeruginosa* the most emerging public health threat. This bacterium is resistant to nearly against almost all antibiotics, including aminoglycosides, cephalosporins, fluoroquinolones and carbapenems [11].

Quorum Sensing – A Promising Target: Quorum sensing is a promising target for the development of new anti-infectives [12]. Bacterial pathogens rely heavily on QS systems to control the expression of genes vital for virulence. Bacterial quorum sensing is regulated *via* small signaling molecules called autoinducers (AIs). In Gram-negative bacteria, QS systems are mainly based on LuxI/LuxR homologues. The LuxI homologs encode an AHL synthase involved in the synthesis of signal molecules, and the LuxR homologs encode the transcription regulatory protein, which, upon binding of the cognate signal molecules, activates the transcription to the QS target genes [13]. At low cell density, the concentration of AHL is low, and unliganded LuxR receptors are intrinsically unstable and rapidly degradable. As cell density increases, the AHL concentration equally increases, and the accumulated AHLs interact with LuxR receptor, leading to stabilization of the protein-ligand complex. The LuxR: AHL complex binds DNA at promoters activating the genes under the control of quorum sensing [14]. Many gram-negative organisms, including *Pseudomonas aeruginosa*, use AHL-type QS signals.

Quorum Sensing in *P. aeruginosa*: Pseudomonas spp., specifically *P. aeruginosa*, uses a complex network of quorum sensing receptors and AIs. The major *P. aeruginosa* receptors are LuxR-type receptors that, following autoinducer binding in the cytoplasm and function as DNA-binding transcriptional activators. There are currently four well-known quorum sensing pathways in *P. aeruginosa*: two LuxR and LuxI-type systems called LasI/R and RhlI/R/the PqsR-controlled quinolone system and the IQS system that functions under phosphate-limiting conditions. However, the bacterium uses predominantly use LasI/LasR and RhlI/RhlR systems as two main pathways for quorum sensing [13, 15]. The systems are organized in a hierarchy with LasR at the top of the cascade. LasR, in complex with 3- oxo-C_{12}-HSL and activates a large regulon of downstream genes that includes the LasI synthase gene, which leads to the production of 3-oxo-C_{12}-HSL.

The LasR–3-oxo-C_{12}-HSL complex also activates the expression of RhlR and RhlI, which encode the second quorum sensing system [15] and the PqsR and PqsABCDH genes, which encode the PQS system. RhlR operates similarly to LasR and, when bound to C_4-HSL, activates its own regulon that includes RhlI and thereby establishes the second auto-induction feed-forward loop. Thus, it is revealed that the quorum sensing mechanism is directly or indirectly regulating the biofilm and virulence trait, in turn, executing the pathogenesis.

Inhibition of Quorum Sensing: Quorum sensing inhibitors (QSIs) are the molecules responsible for inhibition of quorum sensing systems, which leads to suppression of biofilm and virulence factors. It includes furanones and their related structural analogs [16], heavy metals [17] bismuth porphyrin complexes [18], glycosylated flavonoids [19], glycol-monoterpenols [20] and nanomaterials [21]. QS inhibitory activity is due to the structural similarity of furanones with AHLs, but some studies also showed that furanones might function through degrading of the LuxR-type protein [22] or lowering the DNA-binding activity of LuxR, the transcriptional regulator protein [23]. Biofilm formation and QS-controlled virulence factors was reduced by furvina, sulphoraphane, and erucin [24, 25].

Anti-quorum Sensing in Medicinal Plant Formulations: In Indian traditional medicine a formulation called Panchvalkal extract (Pentaphyte P5-capsule form) prepared with mixtures of bark extracts of *Ficus racemosa*, *Albizzia lebbec*, *Ficus bengalensis*, *Ficus lacor* and *Ficus religiosa* exerts anti-virulence effects by disrupting the QS mechanism [26]. Ethanol extract of traditional Thai herbal formulation "Ya-Samarn-Phlae" containing equal proportions of *Oryza sativa* L. (seed), *Curcuma longa* L. (rhizome), *Areca catechu* L. (seed) and *Garcinia mangostana* L. (pericarp) shows significant anti- Pseudomonas biofilm activity [27]. Notably, flavonoids and certain terpenoids containing plant extracts were found to show remarkable quorum sensing inhibition against *P. aeruginosa*. Aqueous extract of the Chinese medicine Yunnan Baiyao showed inhibitory activity against the virulence of *P. aeruginosa* [28].

Medicinal Plant Extracts against Quorum Sensing: Various plants have been identified with the potential to disrupt bacterial quorum sensing (QS), which plays a key role in the regulation of virulence in many gram-positive and gram-negative bacteria [29]. Pyocyanin was remarkably reduced by *Aegle marmelos*. Enhanced cell adhesion inhibition was shown by *Cynodon dactylon* [30]. Rosina Khan has been reported that ethanol fraction of root of *Zingiber officianalis* showed high antiquorum activity [31]. Ethanol extracts of leaves of *Mangifera indica*, *Cassia alata*, plant parts of *Centilla asiatica*, inhibited QS regulated phenotypes, a significant reduction in swarming [32, 33].

Ethyl acetate fraction of *Parkia javanica* fruit extract (PJE) and Onion peel (ONE) inhibited the QS-mediated biofilm formation, EPS (Extracellular polymeric substances) production and swarming motility, elastase, pyocyanin production [34, 35]. Chloroform and petroleum extract of *O. hadiense* [36] and the extract of *T. bellerica* has reduced the production of pyocyanin, exopolysaccharide, and biofilm formation in *P. aeruginosa* strains [37]. Dichloromethane extract of fig leaf inhibited QS regulated phenotypes [38].

Gallic acid, catechin, ellagic acid, chlorogenic acid, quercetin, and kaempferol were identified in the Dichloromethane fraction of *Camellia nitidissima* flowers [39]. The aqueous leaf extract of *Psidium guajava* (GLE), *Centella asiatica* inhibits swarming motility of *Pseudomonas aeruginosa* [40, 32]. Reverse phase-solid phase extraction of aqueous leaf extract of *Cassia alata* inhibited biofilm formation of *Pseudomonas aeruginosa* [41]. Plants from 61 distinct families were assessed for quorum sensing especially plants belonging to the families Fabaceae, Lamiaceae, Combretaceae, Myrtaceae, Zingiberaceae are widely studied, and they potentially inhibit quorum sensing **Table 1**.

Phytochemicals as Quorum Sensing Inhibitors: Major flavonoids, namely, quercetin, quercetrin, kaempferol, myricitin [42, 43], flavanones like naringenin, eriodictyol and taxifolin [44], baicalin [45, 34], eugenol [46], cassipoural [47], flavonoids [48] shows quorum sensing inhibitory activity. Coumarin, a natural plant phenolic compound, Cinnamon [49, 50], Oleanolic aldehyde coumarate (OALC), a novel bioactive compound obtained from extracts of *Dalbergia trichocarpa* bark [51], 6-gingerol, a pungent oil of fresh ginger and Rosmarinic acid shows inhibition against *Pseudomonas aeruginosa* [52, 53]. Virulence factor production was suppressed by administration of flavonoids to *P. aeroginosa*. Especially structure activity relationship reveals that to inhibit LasR / RhlR, two hydroxyl moieties present in the flavone-A ring backbone is important [54]. Extracts of cauliflower, celery salt, chervil, garden cress, lemongrass, radish, thyme, water cress shows positive result QSI screening [55]. Mortality of *C. elegans* was inhibited by aqueous extracts of *Conocarpus erectus*, *Callistemon viminalis*, *Bucida buceras* [56]. Essential oils of cinnamon, lavender, and peppermint showed anti-QS activity [31].

Table 1 lists various plant extracts tested for anti-quorum sensing efficacy. Natural products from plant sources specifically tested for anti-quorum sensing efficacy against *P. aeruginosa* are listed in **Table 2**.

TABLE 1: MEDICINAL PLANTS AGAINST *PSEUDOMONAS AERUGINOSA*

S. no.	Name of the Plant	Family	Active components / Compounds	Part(s)	Solvent(s)	MIC mg/ml	Effects	Reference
1	*Aarmoracia rusticana*	Brassicaceae	Iberin	-	Ethyl acetate, methanol, water	-	Inhibited expression of the lasB-GFp and RHLA-GFP genes in the *P. aeruginosa*	55
2	*Acer palmatum*	Sapindaceae	ND	Leaves	Methanol (99%)	-	Anti-infection activity in *C. elegans* model, attenuate the virulence of *P. aeruginosa* PAO1	57
3	*Acer pseudosieboldianum*	Sapindaceae	ND	Leaves	Methanol (99%)	-	Anti-infection activity in *C. elegans* model, attenuate the virulence of *P.aeruginosa* PAO1	57
4	*Aegle marmelos*	Rutaceae	Pentadecanoic acid, 14-methyl-, methyl ester, Hexadecenoic acid, ethyl ester, l-(+) Ascorbic acid 2,6- dihexadecanoate, oleic acid, 9-Octadecanoic, (E), Hexadecenoic acid,2,3-dihydroxypropyl ester(n)-9-Octadecanoic, (Z)-,2-hydroxy-1(hydroxymethyl)ethyl ester	Leaves	Ethanol	-	Maximum reduction of pyocyanin production	30
5	*Ageratina adenophora*	Asteraceae	Sesquiterpenes, alkaloids, Coumarins	Leaves	95% Ethanol	-	QSI only on the swarming motility but not in pyocyanin production	48
6	*Allium cepa*	Amaryllidaceae	7-keto-(5,6-di-hydro)- β - Sistosterol	Husk	Hydro acetone (70%)	ND	Significant reduction on pyocyanin and biofilm induction, inhibited swimming motilities	58
7	*Allium cepa*	Amaryllidaceae	Quercetin 4-O-β-D glucopyranoside	Peel	Ethyl acetate	0.500 (cv) 0.800 (p.a)	Inhibition of QS controlled virulence Factors (violacein, elastase, pyocyanin, biofi lm), bind at active sites of Vfr, LasR	35
8	*Allium sativum*	Amaryllidaceae	-	Cloves	Normal Saline	-	Lowered renal bacterial counts and protected mouse kidney from tissue destruction. *In-vitro* data showed decreased elaboration of virulence factors and reduced production of quorum- sensing signals	59
9	*Aloe barbadensis*	Liliaceae	-	Leaves	1:1 acetone, Water	-	Inhibition of swarming	60

10	*Alstonia scholaris* (L.) R. Br.	Apocynaceae	3,5,7-trihydroxy flavone	Leaves	Methanol	-	Isolated TF reduced biofilm, pyocyanin, proteolytic, swimming, EPS	61
11	*Alstonia scholaris* (L.) R. Br. (Palay)	Apocynaceae	Alkaloids, Tannins, Triterpenoids, Flavonoids, Phenolic acid	Leaves	95% Ethanol	-	QSI only on the swarming motility but not in pyocyanin production	48
12	*Amomum tsao-ko crevost et lemaire*	Zingiberaceae	tsaokoaryline	Fruits	Ethanol: Water (80:20) Methanol	2.0	Inhibition of biofilm, violacein, swarming motility	62
13	*Amphypterygium adstringens*	Anacardiaceae	Anacardic acids mixture	Stem bark	Hexane	-	Inhibition of pyocyanin, rhamnolipid, elastase, violacein production	63
14	*Anadenanthera colubrina*	Fabaceae	Tannins	Stem bark	Water	2.5	Inhibit biofilm formation via bacteriostatic properties	64
15	*Ananas cosmosus*	Bromeliaceae	-	Fruits	Water	-	reduced biofilm, LasB activity, violacein formation, LasA enzyme	65
16	*Andrographis paniculata*	Acanthaceae	-	All	*Chloroform, Methanol, Water	5.0	Significant reduction of QS-controlled virulence factors by chloroform, methanol extracts	66
17	*Andrographis paniculata*	Acanthaeceae	-	Leaves	70% ethanol	1.0	Inhibition of QS virulence factors	67
18	*Andrographis paniculata*	Acanthaceae	-	Herbs	Water	0.5	Reduction in pyocyanin pigment, protease, elastase production, and biofilm formation	68
19	*Anogeissus accuminata*	Combretaceae	N Hexadecenoic acid, squalene, phytol, betulin, oleyl alcohol, α -tocopherol	Plant material	Methanol	1.0	Significantly reduce violacein, elastolytic activity, EPS, virulence factors	69
20	*Anogeissus leiocarpus*	Combretaceae	-	Stem	Methanol	0.1	Down streaming RHLR gene, reduction of pyocyanin	9
21	*Areca catechu*	Palmae		Seed	1:1 acetone	-	Interfere with QS, reduced the development	70
22	*Artocarpus altilis*	Moraceae	-	Flower	70% ethanol	0.5	Reduced swimming pyocyanin, LasA staphylolytic	67
23	*Aster bakeranus*	Asteraceae	-	Root	Ethyl acetate	2.0	Activity in cell attachment Assay, inhibition of biofilm growth	71
24	*Ayapana triplinervis* (Vahl)	Asteraceae	Coumarins, Tannins, Phenols, Flavonoids, Alkaloids	Leaves	95% Ethanol	-	QSI on swarming motility and pyocyanin production	48
25	*Azadirachta indica*	Meliaceae	Pentadecanoic acid, 14-methyl-methyl ester. 8, 11-Octadecadienoic acid, methyl ester. 10-Octadecadienoic acid, methyl ester. Ethanol, 2-(9-octadecenyloxy)z- Oleic acid. [60] Hexadecanoic acid,1- (hydroxymethyl)1-2-ethannediyl ester. 9-Octadecenoic acid(z)-,2-hydroxy-1 (hydroxymethyl) ethyl ester.	Leaves	95% ethanol	-	Reduced biofilm formation	30
26	*Bidens pilosa*	Asteraceae	Flavonoids, Terpenoids	Leaves	95% Ethanol	-	QSI on swarming, pyocyanin	48
27	*Brassica oleracea*	Brassicaceae	-	Herb	Distilled Water	-	Significantly inhibited QS	72
28	*Brassica oleracea*	Brassicaceae	Sulforaphane, Erucin	-	Water	-	Sulforaphane and erucin effectively bind LASR, resulting	25

							in inhibition of QS activation	
29	*Brassica oleracea*	Brassicaceae	Sulphoraphane	Flower	Ethyl acetate	0.008	Inhibit biofilm, pigment formation	73
30	*Bucida buceras*	Combretaceae	-	NM	Water	-	Inhibition of LasA protease, LasB elastase, pyoverdin, biofilm formation, QS genes ,QS controlled factors	56
31	*Callistemon lanceolatus*	Myrtaceae	-	Leaves	95% Ethanol	-	Inhibition of violacein, increase in pyoverdine	65
32	*Callistemon viminalis*	Myrtaceae	-	NM	Water	-	Inhibition of LasA protease, LasB elastase, pyoverdin, biofilm formation, QS gene expression, QS controlled factors	56
33	*Camellia nitidissima*	Theaceae	Gallic acid, Catechin, Ellagic acid, Chlorogenic acid, Quercetin, Kaempferol	Flowers	(ethanol (95%)) Dichloro Methane	0.067 0.024 0.020	Downregulated the expressions of LASR, RHLR, inhibited swarming, swimming, pyocyanin	39
34	*Camellia sinensis* L.	Theaceae	Tea polyphenols, Catechins	Leaves	Water	0.781	Total proteolytic, elastase, swimming, biofilm formation eas reduced, reduction of *p. aeruginosa* pathogenecity in *C. elegans*, colony forming units in wound area decreased	74
35	*Capparis spinosa*	Capparaceae	-	Fruit	Methanol	2.0	Inhibited violacein, swimming, swarming, rhamnolip ids, biofilm	75
36	*Cassia alata* L.	Fabaceae	Quercetin, Quercetrin and Kaempferol	Leaves	Ethanol, Methanol And Ethyl acetate (bioassay guided fractionation)	0.4	Inhibition of violacein production, biofilm formation	41
37	*Cenchrus ciliaris*	Poaceae	-	Leaves	Methanol Water	2.0 4.0	Activity in cell attachment assay, inhibition of biofilm growth	71
38	*Centella asiatica*	Apiaceae	-	NA	90%Ethanol (Ethyl acetate Fraction)	0.4	Inhibition of pyocyanin, elastolytic, proteolytic, swarming, biofilm	32
39	*Centella asiatica*	Apiaceae	-	Leaves	70% ethanol	0.5	Reduced swimming, swarming, twitching	67
40	*Centratherum punctatum*	Asteraceae	1-Oxo-3, 10-epoxy-5 hydroxy-8-metacryloyloxy-germacra- 2,4(15),11(13)-trien-6,12-olide. 1-Oxo-3,10-epoxy-8-methacryloyloxy- 15-hydroxygermacra 2, 4, 1 1(13)-trien-6,12-olide. 1-Oxo-3,10-epoxy-8-epoxymethacryloyloxy-15-hydroxygermacra-2,4,11(13)-trien- 6,12-olide. 1-Oxo-3,10-epoxy-5-hydroxy-8- angeloyloxy-germacra-2, 4(15),11(13)-trien-6, 12-olide; 1-Oxo-3, 10-epoxy-8-angeloyloxy-15- hydroxyl-germacra-2, 4, 11(13)-trien-6, 12-olide; 1-Oxo-3, 10-epoxy-5-hydroxy-8-tigloyloxy-germacra-2, 4(15), 11(13)- trien-6,12-	Aerial Parts	-	-	Inhibited elastase, biofilm formation	76

			olide.					
41	*Cersis chinensis*	Fabaceae	ND	Leaves	Methanol	ND	Anti-infection activity in *C. elegans* model, attenuate the virulence of P. aeruginosa PAO1	57
42	*Cestrum nocturnum*	Solanaceae	Alkaloids, flavonol	Leaves	95% Ethanol	-	QSI on pyocyanin, swarming	48
43	*Chamaesyce hypercifolia*	Euphorbiaceae	-	NM	Water	-	Inhibition of QS genes and QS-controlled virulence factors	56
44	*Citrus paradisi* Macfadyen Rio red	Rutaceae	Dihydroxy -bergamottin and bergamottin	Fruit (juice)	Ethyl acetate	9.5	Inhibition of AI-1,AI-2, significantly affected biofilm	77
45	*Citrus paradisi* Marsh white	Rutaceae	Dihydroxy -bergamottin and bergamottin	Fruit (juice)	Ethyl acetate	9.5	Inhibition of AI-1,AI-2, significantly affected biofilm	77
46	*Citrus sinensis*	Rutaceae	-	Seeds	95% Methanol	-	Significant elimination of pyocyanin formation and biofilm development	78
47	*Cnidium monnieri*	Apiaceae	-	Seeds	1:1 acetone	-	Inhibition of swarming	60
48	*Coffee arabica*	Rubiaceae	Sesquiterpenes, Amides, Sterols	Husk	Hydro distillation	-	Inhibited biofilm, swarming, extracellular polymeric substances	79
49	*Combretum albiflorum*	Combretaceae	[(2R,3S)- 2-(3,4-dihydroxyphenyl)- 3, 4dihydro-1(2H)-benzopyran -3, 5, 7-triol]	Bark	Water	-	Negative effect on pyocyanin, elastase, biofilm, QS-regulated genes	43
50	*Commiphora leptophloeos*	Burseraceae	Tannins	Bark	Water	1.0	Inhibit biofilm formation via bacteriostatic properties	64
51	*Conocarpus erectus*	Combretaceae	-	NM	Water	-	Inhibition of LasA protease, LasB elastase, pyoverdin, biofilm formation, QS genes, QS controlled factors	56
52	*Coptis chinensis*	Ranunculaceae	-	Plant material	Water	2.0	Inhibition of QS regulated virulence factors	80
53	*Cordia gilletii* de wild	Boraginaceae	-	Root barks,leaves	Dichloromethane Methanol	-	Quench the production of pyocyanin, a QS-dependent virulence factor, reduce gene expression lasB, rhlA, lasI, lasR, rhlI and rhlR), biofilm	81
54	*Coriandrum sativum*	Apiaceae	-	Fruits	95% Methanol	-	Significant elimination of pyocyanin formation and biofilm development	78
55	*Cornus controversa*	Cornaceae	-	-	80% ethanol	-	Strongest anti-biofilm activity, suppressed soft rot of cabbage	82
56	*Cortex phillodendri chinensis*	Rutaceae	-	Herbs	Water	0.5	Reduction in pyocyanin pigment, protease, elastase production and biofilm formation	68
57	*Cryptocarya lattifolia*	Lauraceae	-	Bark	Ethyl acetate Hexane	2.0 4.0	Activity in cell attachment assay, inhibition of biofilm growth	71
58	*Cuminum cyminum*	Apiaceae	Methyl eugenol	Seeds	Methanol	-	Reduce AHL ,biofilm,violacein	83
59	*Curcuma longa*	Zingiberaceae	-	Spice	Distilled Water	-	Significantly inhibited QS,decreased	72

60	*Curcuma longa*	Zingiberaceae	Heptadecanoic acid, 16-methyl-methyl ester. 10-Octadecadienoic acid, methyl ester. 6-(p.Toly)-2-methyl-2-heptenol. 7-Oxabicyclo (4.1.0) heptane,1-(1,3- dimethyl-1,3-butadienyl)-2, 2, 6-trimethyl-(E). Acetic acid,3-hydroxy-6-isopropenyl- 4,8a-dimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl ester. 7-(1,3-dimethylbuta-1,3-dienyl)-1, 6, 6- trimethyl-3, 8-dioxatricyclo [5.1.0.0(2,4)]) loctane	Leaves	95% ethanol	-	PAO1 swarming Reduced biofilm formation	30
61	*Cymbopogon citratus*	Poaceae	-	-	Ethyl acetate, methanol, water	-	Inhibited expression of the lasB-GFP and RHLA-GFP genes in the *P. aeruginosa*	55
62	*Cynodon dactylon*	Poaceae	2-penta,6,10,14-trimethyl, 1-Dodecanol,3,7,1 1-trimethyl, Hexadecenoic acid-ethyl ester, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, Ethyl oleate, Heptadecanoic acid 15-methyl-ethyl ester, Eichosanoic acid-ethyl ester	Leaves	95% Methanol	-	Enhance cell adhesion inhibition	30
63	*Dalbergia trichocarpa*	Fabaceae	3β-hydroxyolean-12-en-28-al 3-p- coumarate (Oleanolic aldehyde coumarate)	Bark	n-hexane	-	Inhibition of gacA by OLAC, reduction of *C. elegans* paralysis	84
64	*Dalbergia trichocarpa*	Fabaceae	3β-hydroxyolean-12-en-28-al 3-p- coumarate (Oleanolic aldehyde coumarate)	Bark	n-hexane	-	Significant reduction of Caenorhabditis elegansparalysis, reduction in fQS-controlled virulence factors including, rhamnolipids, p yocyanin, elastase And extra cellular polysaccharides as well as twitching and swarming motilities	51
65	*Decaspermum fruticosum*	Myrtaceae	-	Leaves	95% Ethanol	-	Inhibition of violacein No effect on virulence factors	85
66	*Derris elliptica* Benth.(Opay)	Fabaceae	Tannins, Alkaloids, Terpenoids	Leaves	95% Ethanol	-	Inhibited swarming motility	48
67	*Elettaria cardamomum*	Zingeberaceae	-	Seeds	95% Methanol	-	Significant elimination of pyocyanin formation and biofilm development	78
68	*Eucalyptus globules*	Myrtaceae	-	-	Ethyl acetate, methanol, water	-	QSI activity, positive in LASB-GFP and RHLA-GFP genes	55
69	*Eucalyptus globulus*	Myrtaceae	Patchoulene Globulol a-phellandrene pentadecanoic acid,14-methyl-methyl ester. 1, 2-benzene dicarboxylic acid, butyl octy ester. 8, 11-Octadecadienoic acid, methyl ester. Ethanol, 2-(9-octadecenyloxy_z- Oleic acid. 2, 3-Dihydroxypropyl elidate. Hexadecanoic acid, 1- (hydroxymethyl)1, 2-	Leaves	95% ethanol	-	Maximum inhibition of QS-mediated virulence factors	30

			ethannediyl ester. 9-Octadecenoic acid (z)-,2-hydroxy-1-(hydroxymethyl)ethyl ester.					
70	*Eucomis autumnalis*	Hyacinthaceae	-	Bulb	Hexane	2.0	Activity in cell attachment Assay, inhibition of biofilm growth	71
71	*Ficus carica*	Moraceae	-	Leaves	Dichloro methane MeOH	-	Inhibition of QS activity	38
72	*Fragaria sp*	Rosaceae	-	Fruits	Distilled Water	-	Decreased pigment formation, swarming	72
73	*Fructus gardenia*	Rubiaceae	-	Herbs	Water	0.5	Reduction inpyocyanin pigment, protease, elastase production, and biofilm formation	68
74	*Galla chinensis*	Anacardiaceae	-	Plant material	Water	2.0	Inhibition of QS regulated virulence factors	80
75	*Ginkgo biloba*	Ginkgogaceae	-	-	Ethyl acetate, methanol, water	-	QSI activity, positive in LASB-GFP and RHLA-GFP genes	55
76	*Gnetum gnemon*	Gnetaceae	-	NA	Hexane, Chloroform Methanol	-	Inhibition of pyocyanin	86
77	*Guiera senegalensis*	Combretaceae	Methyl gallate (Isolated)(3,4,5-tri hydroxy benzoate)	Galls	Methanol	2.5 (Cv) 5.0 (Pa)	Inhibiting violacein, pyocyanin	87
78	*Hemidesmus indicus*	Apocynaceae	-	Root	70% ethanol	-	Inhibiting violacein, reduction in swarms	33
79	*Holarrhena antidysentrica*	Apocynaceae	-	Bark	70% ethanol	-	Inhibiting violacein, reduction in swarms	33
80	*Hydnoaa africana*	Hydronaceae	-	Bark	Methanol	4.0	Activity in cell attachment assay, inhibition of biofilm growth	71
81	*Hypericum connatum*	Guttiferae	Rutin and Apigen, caffeic acid, epicatechin Epicatechin, and p-coumaric acid, ferulic acid, luteolin, quercetin, hyperoside, chlorogenic acid, gallic acid	NA	Ethanol, Ethyl acetate	-	Inhibited production of violacein	88
82	*Hypericum perforatum*	Hypericaceae	-	Aerial parts	Methanol, ethanol, acetone	-	Inhibited LASIR signalling pathways	89
83	*Jasminum sambac*	Oleaceae	-	Flower Leaf	95% ethanol	3.0	Weak anti-quorum sensing activity	90
84	*Lagerstroemia Speciosa*	Lythraceae	-	Fruit	80% ethanol	-	Downregulation of quorum sensing (QS)-related genes (las and rhl), AHL, LasA protease, LasB elastase and pyoverdine	91
85	*Laserpitium ochridanum*	Apiaceae	Sabinene, Viridiflorol, α-Pinene, Terpinen-4-ol	Plant material	Methanol, Ethanol Distilled water	0.5	Significant reduction of biofilm, pyocyanin, slight reduction in swimming and twitching motility	92
86	*Laurus nobilis*	Lauraceae	-	Leaves	95% methanol	-	Significant elimination of pyocyanin formation and biofilm development	78
87	*Laurus nobilis*	Lauraceae	-	Fruit Leaves Bark Flower	95% ethanol	2.0 0.5 3.0 1.0	Weak to good activity	90
88	*Lepidium sativum*	Brassicaceae	-	-	Ethyl acetate, methanol, water	-	Inhibited expression of the lasB-gfp and rhlA-gfp genes in the P. aeruginosa	55
89	*Lessertia*	Fabaceae	-	Leaves	Ethyl acetate,	4.0	Activity in cell	71

	fruitescens				Hexane	4.0	attachment Assay, inhibition of biofilm growth	
90	*Lilium brownie*	Liliaceae	-	Bulb	1:1 acetone Water	-	Inhibition of violacein, swarming	60
91	*Mallotus roxburghianus* Muell. Arg	Euphorbiaceae	Sulphurous acid,2-propyl tridecyl ester, betulin ,dihydrotochysterol, α -tocopherol	Plant material	Ethanol	0.75	Significantly reduce violacein, elastolytic activity, EPS, virulence factors	69
92	*Mangifera indica*	Anacardiaceae	-	Leaves	70% ethanol	-	Inhibiting violacein,reduction in swarms	33
93	*Mangifera indica*	Anacardiaceae	-	Leaves	70% ethanol	1.0	Inhibition of bacterial motility	67
94	*Mangifera indica*	Anacardiaceae	Pyrogallol, Benzoic acid,4-hydroxy, n- hexadecanoic acid,4H-pyran-4-one,2,3-dihydro-3,5-dihydroxy-6 methyl	Leaves	benzene, ethyl acetate, acetone, methanol and ethanol	2.0	Inhibition of biofilm, reduction in QS virulence factors	93
95	*Manilkara zapota*	Sapotaceae	-	Fruits	Water	-	Reduced biofilm formation, violacein, LasA Staphylolytic, increased pyocyanin	65
96	*Medicago truncatula*	Fabaceae	-	Seedlings	Ethyl acetate Methanol	-	Inhibit AHLQS substances	94
97	*Melaleuca cajuputi*	Myrtaceae	-	Leaves	95% Ethanol	-	Inhibition of violacein, increased pyoverdin	84
98	*Melicope lunu-ankenda* (Gaertn.)	Rutaceae	-	NA	Hexane, Chloroform and Methanol	-	Disrupted pyocyanin synthesis, swarming motility and expression of lecA::lux	95
99	*Muntingia calabura*	Muntingiaceae	-	Leaves	70% ethanol	1.0	Reduced bacterial motility	67
100	*Musa paradiciaca*	Musaceae	-	Pseudo Stem	Water	-	Reduced biofilm formation,no significant effect on biofilm	65
101	*Myracrodruon urundeuva*	Anacardiaceae	Tannins	Bark	Water	4.0	Inhibit biofilm formation via bacteriostatic properties	64
102	*Myristica cinnamomea*	Myrtaceae	Malabaricone	Bark	Methanol	-	Inhibited the quorum sensing- regulated pyocyanin production and biofilm formation	96
103	*Ocimum hadiense*	Lamiaceae	ND	NA	Aq.ethanol Pet.ether Chloroform	6.25 3.125 6.25	Highest reduction in LasA activity, decrease in pyocyanin	36
104	*Ocimum sanctum*	Lamiaceae	-	Leaves	Water	-	No significant effect on biofilm, reduced violacein, LasB, increased pyocyanin	65
105	*Ocimum tenuiflorum*	Lamiaceae	9-Octadecene, 1, 1-(1,2-ethanediylbis(oxy))bis-,(ZZ). Ethyl 9,9-diformlnona-2,4,6,8-tetraenoate	Leaves	95%ethanol	-	Reduced biofilm formation	30
106	*Oreganum vulgare*	Lamiaceae	-	Herb	Distilled Water	-	Decreased swarming, violacein	72
107	*Oreocnide trinervis* (Wedd.) Miq.	Urticaceae	Flavonoids	Leaves	95% Ethanol	-	Inhibited swarming, pyocyanin	48
108	*Oscimum bascilicum*	Lamiaceae	-	Herb	Distilled Water	-	Decreased swarming, violacein	72
109	*Ostostegia fruticosa*	Lamiaceae	ND	NA	Aq.ethanol, Pet. ether Chloroform	6.25 6.25 3.125	Highest reduction in pyocyanin by chloroform extract, best anti swarming activity	36
110	*Panax notoginseng*	Araliaceae		flower,root	1:1 acetone	-	Interfere with QS, reduced the development	70
111	*Panax pseudoginseng*	Araliaceae	-	Root	1:1 acetone Water	-	Inhibition of violacein, swarming	60
112	*Panax*	Araliaceae				-	Not inhibited the	97

	pseudoginseng		-	Root	-		growth of bacteria, enhance extracellular protein production, supressed LasA, LasB, AHL	
113	*Parkia javanica*	Fabaceae	Baicalein, Quercetin, Chrysin	Fruits	Methanol Ethyl Acetate (fraction)	0.03	Attenuation in swarming, proteases, pyoverdine, pyocyanin, PJE as a whole shows good activity than the individual compounds	34
114	*Perilla frutescens*	Lamiaceae	-	Leaves	Dichloro methane MeOH	-	Inhibition of QS activity	38
115	*Phyllanthus amarus*	Phyllanthaeceae	-	NA	Hexane, Chloroform * Methanol	-	Incerasing concentrations reduced pyocyanin, swarming, lecA:lux expression	98
116	*Piper betle*	Piperaceae	-	NA	Hexane. Chloroform Methanol	-	Inhibition of pyocyanin, potent anti quorum sensing activity	86
117	*Piper nigrum*	Piperaceae	-	NA	Hexane, Chloroform Methanol	-	Inhibition of swarming, good anti quorum sensing activity	86
118	*Pistacia atlantica*	Anacardiaceae	Rutin, Myricetin, Kaemferol-3-O- rutinoside, 3-O-rutinoside, isoquercetrin	Leaves	Methanol	0.5	Active components had high affinity for LASR protein, high anti-QS activities	99
119	*Pisum sativum*	Fabaceae	-	Seedling	Methanol, Ethanol	-	Inhibition of violacein, reduced swarming	100
120	*Plantago asiatica*	Plantaginaceae	ND	Whole herb	95% ethanol	0.016	Inhibition of virulence factors (pyocyanin, rhamnolipids, protease, alginate)	101
121	*Platostoma Rotundifolium* (Briq.) A.J.Pato	Lamiaceae	Cassipourol β-sitosterol α-amyrin	Aerial parts	n-hexane, Dichloro methane, Ethyl acetate,	4.0	Terpenoids reduce production of total EPS, promote flagella-dependent motilities	47
122	*Plectranthus tenuiflorus*	Lamiaceae	phytol, mosloflavone, N-hexadecanoic acid, Beta-D-glucopyranose, 1,6-anhydro and gamma sitosterol	Leaves	Methanol	0.75	Inhibit quorum sensing regulatory genes expression in LAS and RHL systems, reduce the production of total exopolysaccharides and promote flagella-dependent motilities	102
123	*Prunus armeniaca*	Rosaceae	-	kernel of seed	1:1 acetone	-	Interfere with QS, reduced the development	70
124	*Psidium guajava*	Myrtaceae	Quercetin-3-O-arabinoside, Quercetin	Leaves	Methanol	0.2	Inhibited pyocyanin production, proteolytic and elastolytic activities, swarming motility and biofilm formation	103
125	*Psoralea corylifolia*	Fabaceae	-	Seeds	70% ethanol	-	Inhibiting violacein, reduction in swarms	33
126	*Punica granatum*	Lythraceae	-	Pericarp	70% ethanol	-	Inhibiting violacein, reduction in swarms	33
127	*Quercus infectoria*	Fagaceae	-	Gall	Absolute Methanol	-	Decreased expresiion of LasA, LasB, Swarming, twitching motility	104
128	*Quercus infectoria*	Fagaceae	-	Gall	Acetone	0.312	Highest anti quorum sensing activity, reduced the pyocyanin, protease, elastase, biofilm	105

							formation	
129	*Quercus virginiana*	Fagaceae	-	NM	Water	-	Inhibition of QS genes and QS-controlled virulence factors	56
130	*Ranunculus multifidus*	Ranunculaceae	-	Root	Methanol	4.0	Activity in cell attachment assay,inhibition of biofilm growth	71
131	*Rhizome coptidis*	Ranunculaceae	-	Herbs	Water	0.5	Reduction in pyocyanin pigment, protease, elastase production, and biofilm formation	68
132	*Rhizophora Murcunata*	Rhizophoraceae	-	Leaves	Methanol	1.0	Inhibition of LasA protease, LasB elastase, total protease, pyocyanin pigment production and biofilm formation	106
133	*Rhizophora apiculate*	Rhizophoraceae	-	Leaves	Methanol	1.0	Inhibition of LasA protease, LasB elastase, total protease, pyocyanin pigment production and biofilm formation	106
134	*Rhoicissus tridentate*	Vitaceae	-	Root	Methanol	2.0	Activity in cell attachment assay, inhibition of biofilm growth	71
135	*Ricinus communis*	Euphorbiaceae	(4-methoxy-1-methyl-2-oxo-1,2- dihydropyridine-3-carboxamide), Acetyl ricininic acid derivative	Seeds	-	-	Good anti-quorum sensing activity	107
136	*Rosa ruguosa*	Rosaceae	Gallic acid (8.32%), Catechin(8.08%), Tannin (3.44%), Epicatechin (18.08%), Quercetin (3.66%), Kaempferol (0.81%), Benzoic acid (6.88%), quercetin glycoside (0.38%), epigallocatechin (13.01%)	Buds	Deionized water	1.8	Inhibited QS controlled virulence production, swarming, biofilm.	108
137	*Rosemaroinus Officinalis*	Lamiaceae	-	Herb	Distilled Water	-	Decreased violacein, pigment production	72
138	*Rosmarinus officinalis*	Lamiaceae	-	Flower Leaf	95% Ethanol	ND 2.0	Weak AQS activity	90
139	*Rrhenum Rhabarbarum*	Polygonaceae	-	Herbs	Water	3.9	Reduction inpyocyanin pigment, protease, elastase production and biofilm formation	68
140	*Rubus eubatus*	Rosaceae	-	Fruits	Distilled Water	-	Inhibited violacein, swarming	72
141	*Rubus ideaus*	Rosaceae	-	Fruits	Distilled Water	-	Inhibited violacein, swarming	72
142	*Sarcandra glabra* (Thunb.)	Chloranthaceae	Coumarins, Flavonoids, Rosmarinic acid, Sesquiterpenoids	Leaves	95% Ethanol	-	QSI on swarming motility	48
143	*Sclerocarya birrea*	Anacardiaceae	-	Stembark	Methanol	-	Anti biofilm activity at sublethal concentration, significantly reduced swarming, virulence Factors (protease, pyoverdin)	109
144	*Smilax china* L.	Smilacaceae	Resveratrol	-	DMSO	-	Relieving oxidative stress, disturbing the TCA cycle, supress virulence	110
145	*Sonchus oleraceus*	Asteraceae	-	Aerial	95% Ethanol	1.5	AQS activity	90
146	*Syzygium*	Myrtaceae	Phytol, Ethyl linoleate and	Fresh		-	Phytochemicals	85

	antisepticum		Methyl linolenate	Leaves	95% Ethanol		reduced rhamnolipid production, inhibition activity over virulence factors	
147	*Syzygium Aromatica*	Myrtaceae	-	Oil	-	-	Reduced biofilm,enhance *C. elegans* survival, reduction in las and rhl regulated virulence factors	111
148	*Syzygium aromaticum*	Myrtaceae	Eugenol b-Caryophyllene, Iso-caryophyllene, Napthalene, 1,2,3,5,6,8a-hexahydro-4, 7-dimethyl-1-(1-methyl ethyl), 1,6-Octadiene-ol-,3,7-dimethyl acetate, a-Caryophyllene, Caryophyllene oxide	Oil	-	-	No activity on pure eugenol,	31
149	*Syzygium aromaticum*	Myrtaceae	-	Clove Buds	Hexane, methanol Chloroform, DMSO	-	Inhibited QS - regulated phenotypes, lec::Alux, pyocyanin (hexane extract), swarming (methanol extract)	112
150	*Syzygium aromaticum* (L.)	Myrtaceae	Eugenol	Flower Buds	NM n-hexane	0.8 (cv) 6.4	Inhibited the production of virulence factors (elastase, pyocyanin, violacein, biofi lm)	113
151	*Syzygium cumini* L.	Myrtaceae	3-N-Hexylthiane s-s-dioxide, Heptacosanoic acid, 3N-Hexylthiolane s-s-dioxide, 3-Methyl 2-(2-Oxopropyl) Furan	Leaves	Methanol	-	Reduction in biofilm formation, virulence factor inhibition	114
152	*Syzygium jambos*	Myrtaceae	Phytol, Ethyl linoleate Methyl linoleate	Leaves	95% Ethanol	-	Phytochemicals reduced rhamnolipid production, inhibition activity over virulence factors	85
153	*Syzygium jambos*	Myrtaceae	-	Leaves	Ethanol	1.0	Strong binding affinity of the phytoconstituents	115
154	*Tecoma capensis*	Bignoniaceae	-	Flower Leaf	95% Ethanol	3.0 2.4	AQS activity	90
155	*Terminalia bellerica*	Combretaceae	1,2-di benzyloxy benzene, pentanoic acid 2,5-furandione, dioxolano[b]tricycle[4.1.0.0 (1.3)]heptan-2-thione	Leaves	Methanol	0.5	Reduced the production of EPS, pyocyanin, biofilm formation	37
156	*Terminalia catappa* L.	Combretaceae	Tannins, polyphenols, flavonoids	Leaves Bark	Methanol	-	Inhibited violacein,maturation of biofilms	116
157	*Terminalia cattappa*	Combretaceae	-	Leaves	70% ethanol	0.5	Inhibition of pyocyanin, bacterial motility, biofilm, LasA protease	67
158	*Terminalia chebula*	Combretaceae	Elagic acid, Methyl S-flavogallonic acid, S-flavogallonic acid, 3, 4, 8, 9, 10-pentahydroxylbenzo (b.d) Pyran-6-one	Fruit	Water Methanol	-	Reduction in Extracellular virulence factors, alginate, biofilm, AHLs	117
159	*Tetrazygia bicolor*	Melastomataceae	-	NM	Water	-	Inhibition of QS genes and QS-controlled virulence factors	56
160	*Thymus* sp Thyme	Lamiaceae	-	Herb	Distilled Water	-	Inhibited violacein, swarming	72
161	*Tinospora cordifolia*	Menispermaceae	-	Stem	Ethyl acetate	-	Inhibited short as well as long acyl-HSLs	118
162	*Trachyspermum copticum*	Apiaceae	-	Plant material	Methanol	2.5	Reduced the pyocyanin, protease,	105

							elastase, biofilm formation	
163	*Tribulus terristris*	Zygophyllaceae	β -1,5-O-dibenzonyl ribo furanose	Root	Methanol (80%)	2.5	Downregulating pigment production, biofilm formation	119
164	*Trigonella foenum - graceum*	Leguminosae	Caffeine(40.82%),methyl 14-methyl penta decanoate(8.22%), palmitic acid(6.41%), 1,2,3,benzenetriol(6.13%), linoleic acid methyl ester(5.58%),capric acid(4.2%), 9,12,15-Octadecatrienoic acid, methyl ester(9.17%)	Seed	Methanol	1.2	Decreased biofilm forming abilities, downregulate lasB gene, enhanced survival of *C. elegans*	120
165	*Trigonella foenum - graceum*	Leguminosae	-	Seedling	Methanol, Ethanol	-	Enhance d pigment production, swarming	100
166	*Vaccinium macrocarpon*	Ericaceae	-	Fruits	Distilled Water	-	Decreased violacein, swarming	72
167	*Vaccinum angustifolium*	Ericaceae	-	Fruits	Distilled Water	-	Decreased violacein, swarming	72
168	*Verbascum sinaiticum*	Scrophulariaceae	ND	NA	aqueous ethanol (70%), Petroleum ether Chloroform	6.25 6.25 3.125	Highest reduction in LasA activity, decrease in pyocyanin	36
169	*Vernonia adoensis*	Asteraceae	-	Bark	Water	4.0	Activity in cell attachment assay, inhibition of biofilm growth	71
170	Vitis sp	Vitaceae	-	Fruits	Distilled Water	-	Decreased violacein, swarming	72
171	*Zataria multiflora*	Lamiaceae	-	Plant material	Methanol	5.0	Reduced the pyocyanin, protease, elastase, biofilm formation	105
172	*Zingiber officinale*	Zingiberaceae	-	Spice	Distilled Water	-	Decreased violacein, swarming	72
173	*Zingiber officinale*	Zingiberaceae	-	Spice	Toluene	-	Decreased production of extracellular polymeric substances, surface biofilm cells formed with ginger extract detached more easily with surfactant	121

TABLE 2: NATURAL PRODUCTS FROM PLANT SOURCES SPECIFICALLY TESTED FOR ANTI-QUORUM SENSING EFFICACY AGAINST *P. AERUGINOSA*

S. no.	Compound name	MIC	Effects	Reference
1	Rosmarinic Acid	-	RA bound to QS regulator RhlR of *P .aeruginosa*	53
2	Coumarin	-	Active against short, medium and long-chain N-acyl-homoserine lactones, suppressed biofilm, phenazine, motility, expression of the RHLI and PQSA	49
3	Caffeine Coffea arabica	-	Inhibit N-acyl homoserine lactone production and swarming	122
4	Hyperoside (modified flavonoid)	-	Inhibited twitching in addition to adhesion, expression of LASI, LASR, RHLI, RHLR, Biofilm formation	123
5	Vanillic acid Caffeic acid Cinnamic acid Ferulic acid	-	Reduced biofilm, pyocyanin	124
6	Phillyrin *Forsythia suspense* Oleaceae	0.5	Decrease in the production of virulence factors-rhamnolipid, pyocyanin, elastase, biofilm formation	125
7	Methyl gallate Pyrogallol Pyrocatechol Resorcinol Phloroglucinol Norfloxacin	0.512 0.064 0.256 2.048 2.048 0.00025	MG supressed both the synthesis and activituy of AHL, restricted biofilm, motility, elastase, proteolytic, pyocyanin, supressed the expression of LASI/R, RHLI/R, PQSA	126
8	Diallyl disulphide	-	Decreased elastase, pyocyanin, biofilm, swarming, DADS	127

	(garlic oil)		down-regulated QS genes (LASI, LASR, RHLI, RHLR, PQSA, PQSR)	
9	Mosloflavone Mosla soochouensis mastuda	0.25	Inhibited pyocyanin, las B, elastase, chitnase, biofilm formation, downregulated gene expression levels of lasI, lasR, rhlI, rhlA, rhlR, chiC, lasB, phzM, toxA, aprA, exoS, algD, pela	128
10	Parthenolide	-	Reduced EPS, biofilm, repressed lasI, rhlI, lasR, rhlR	129
11	Baicalein, Quercetin, Chrysin	0.075 0.100 0.025	Attenuation in swarming, proteases, pyoverdine, pyocyanin, PJE as a whole shows good activity than the individual compounds	34
12	Phytol, Ethyl linoleate Methyl linoleate	-	Phytochemicals reduced rhamnolipid production, inhibition activity over virulence factors	86
13	*Baicalin*	1.024	Enhanced clearance of infection in *C. elegans*, a significant decrease in OS signalling molecules	45
14	Resveratrol	-	Relieving oxidative stress, disturbing the TCA cycle, suppress virulence	111
15	*D-(+)raffinose pentahydrate 6-gingerol Farnesol L-ascorbic acid Myricetin	1.0	Efficient biofilm inhibition of *P. aeruginosa*, reduced the concentration of the second messenger, cyclic diguanylate	52
16	*Eugenol Clove bud oil*	-	Decrease in transcription of pqsA but not in las I,rhlI levels	46
17	Proanthocyanidins	-	Reduced AHL level of bacteria, cerPAC effectively reduced the level of AHLs.	130
18	Phloretin Chrysin Baicalein Quercetin 7, 8-dihydroxy flavone	-	Prevented LasR-3 OC_{12}HSL DNA binding by 50%	54
19	Resveratrol Oxyresveratrol Piceatannol Pterostilbenoids Chrysotobienzyl Erianin Chrysotoxine Gigantol Chrysotoxene Confusarin	-	Stronger AQS activity, significant reduction of pyocyanin, supressed the expression of QS induced genes (lasI, lasR, rhlI, rhlR) No QSI effect	131
20	6-gingerol	-	Reduced biofilm, several virulence factors, mice mortality repressed QS induced genes	52
21	Cinnamon oil	0.0001	Inhibition of virulence factors	50
22	Eugenol	0.8(cv) 6.4	Inhibited the production of virulence factors (elastase, pyocyanin, violacein, biofilm)	114
23	Iberin	-	Inhibited expression of the lasB-gfp and rhlA-gfp genes in the *P. aeruginosa*	55
24	Andrographolide	-	Lowers mexB mRNA expression, reduced expression of MexAB-OprM efflux pump	132
25	Apigenin Eriodictyol Kaempferol Luteolin Myricetin Naringenin Naringin Quercetin Taxifolin Chalcone	-	Inhibited pyocyanin production (except naringin), flavanones reduced pyocyanin and elastase	44
26	Curcumin	0.030	Downregulation of 31 quorum sensing (QS) genes, reduce pathogenicity, biofilm	133
27	Dihydroxy Bergamottin (isolated) Bergamottin (isolated)	-	Inhibition of AI-1, AI-2, significantly affected biofilm	77

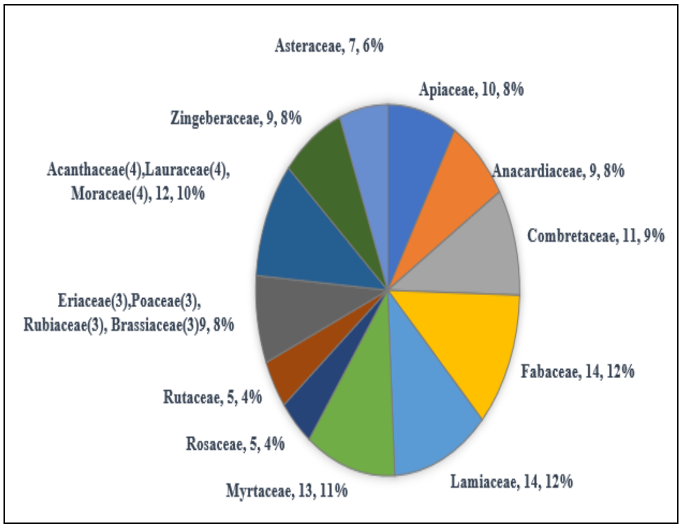


FIG. 1: COMPARISON OF ANTI-QUORUM SENSING ACTIVITY OF VARIOUS PLANT FAMILIES AGAINST *PSEUDOMONAS AERUGINOSA*

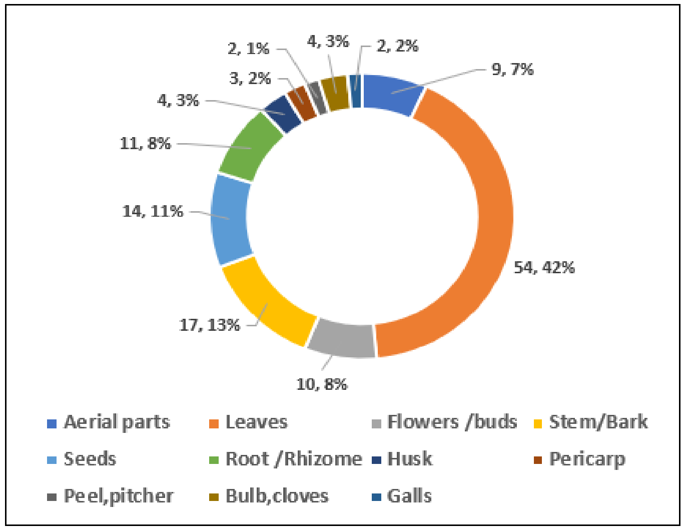
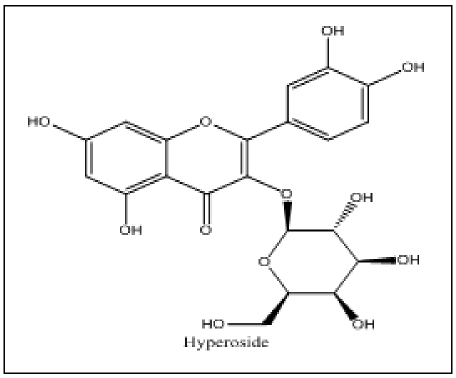
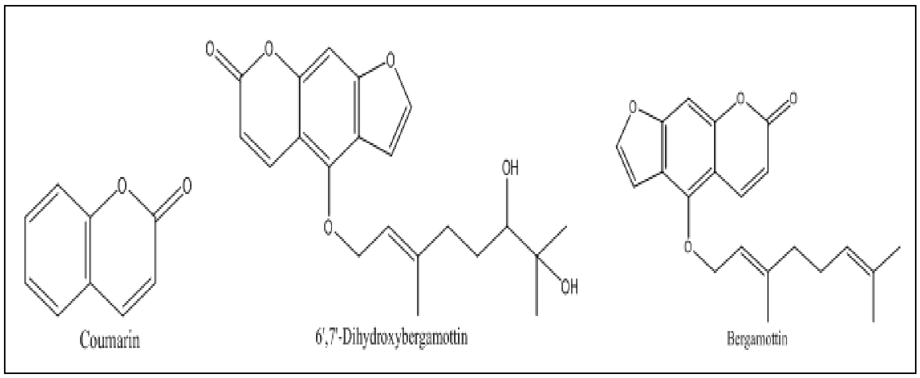


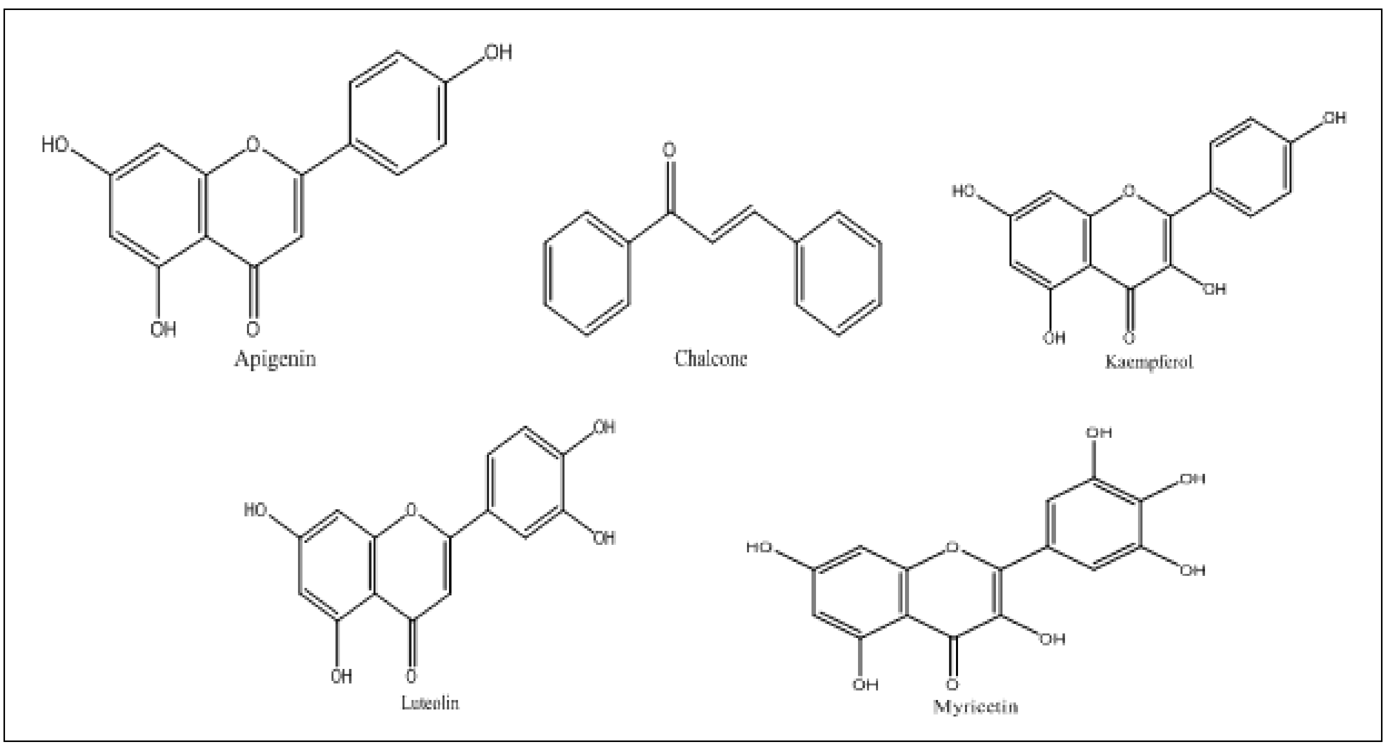
FIG 2: PERCENTAGE OF PLANT PARTS USED IN ANTI-QUORUM SENSING STUDIES AGAINST *PSEUDOMONAS AERUGINOSA*

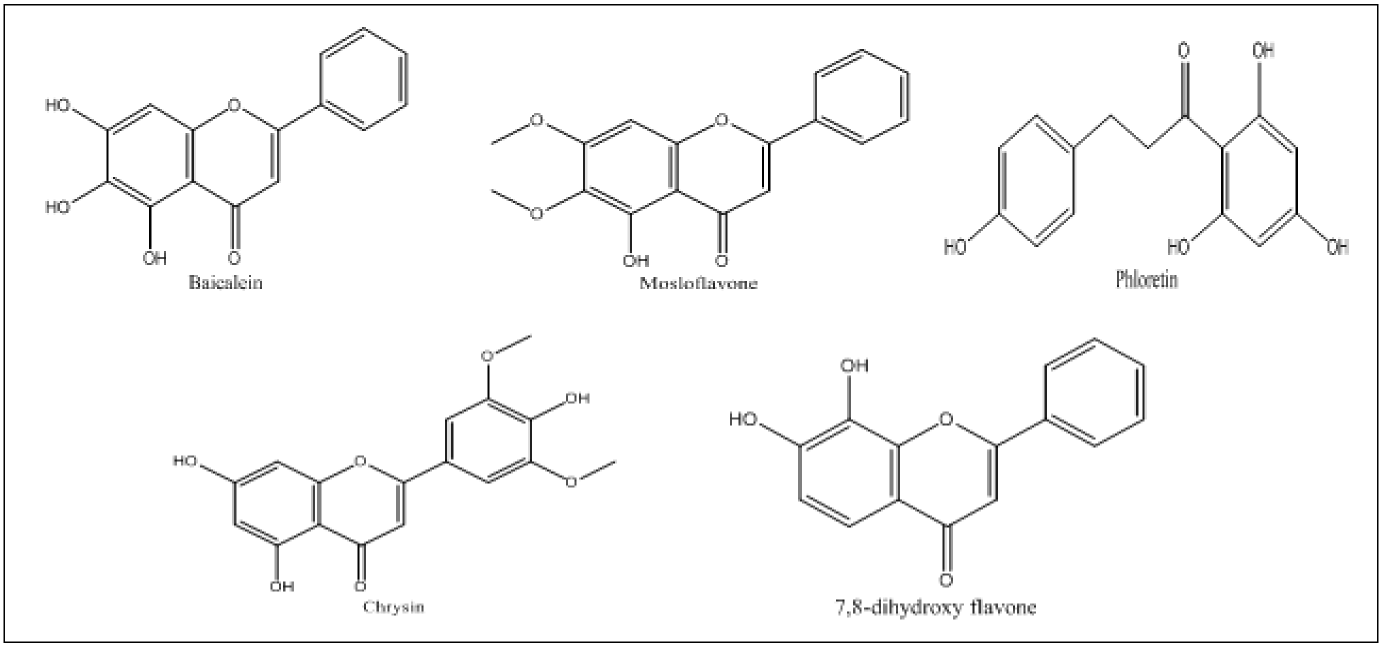


FLAVONOIDS



COUMARINS/FUROCOUMARINS





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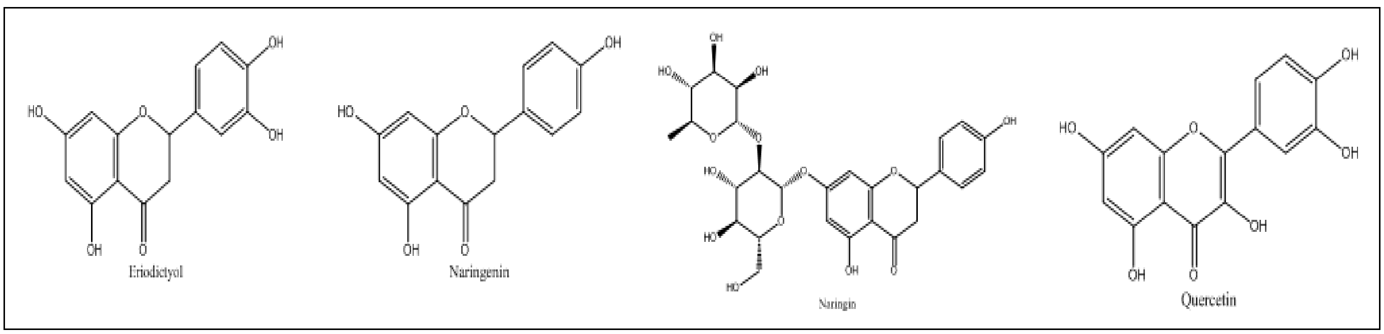
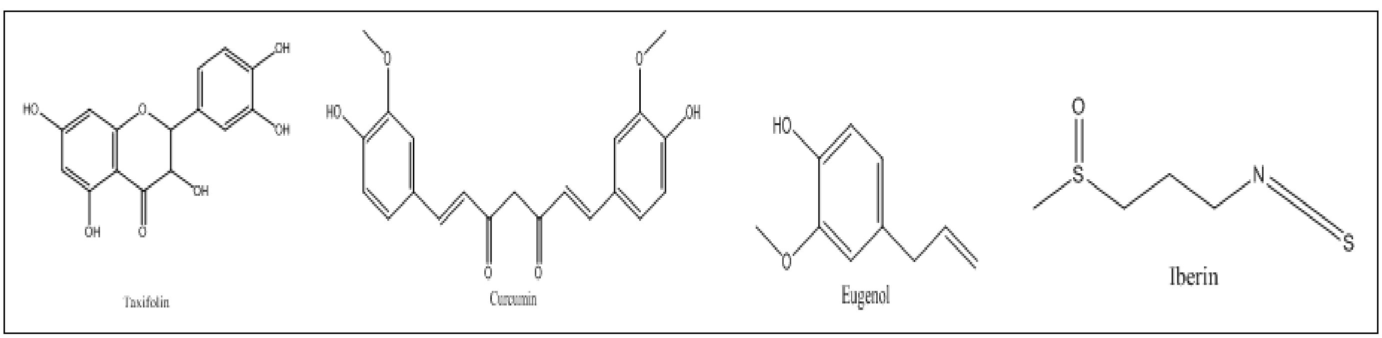
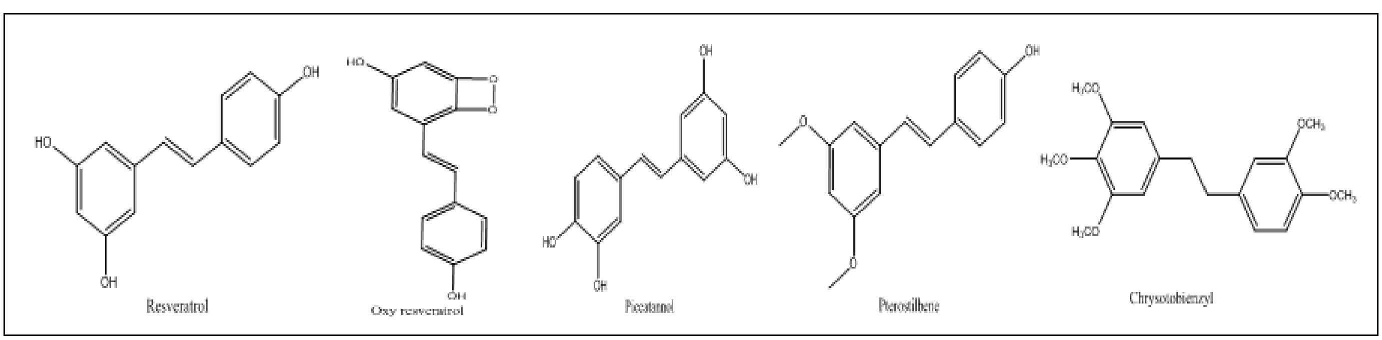


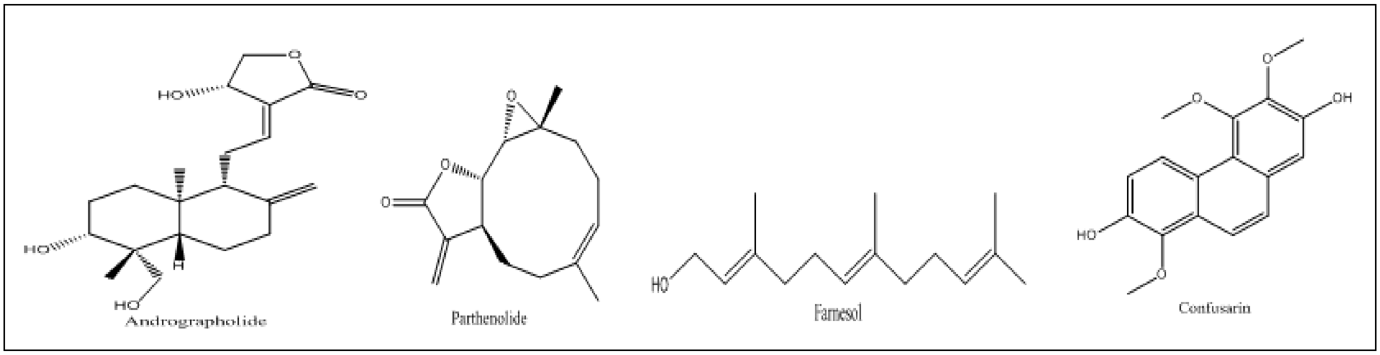
FLAVONONES, FLAVONOLS



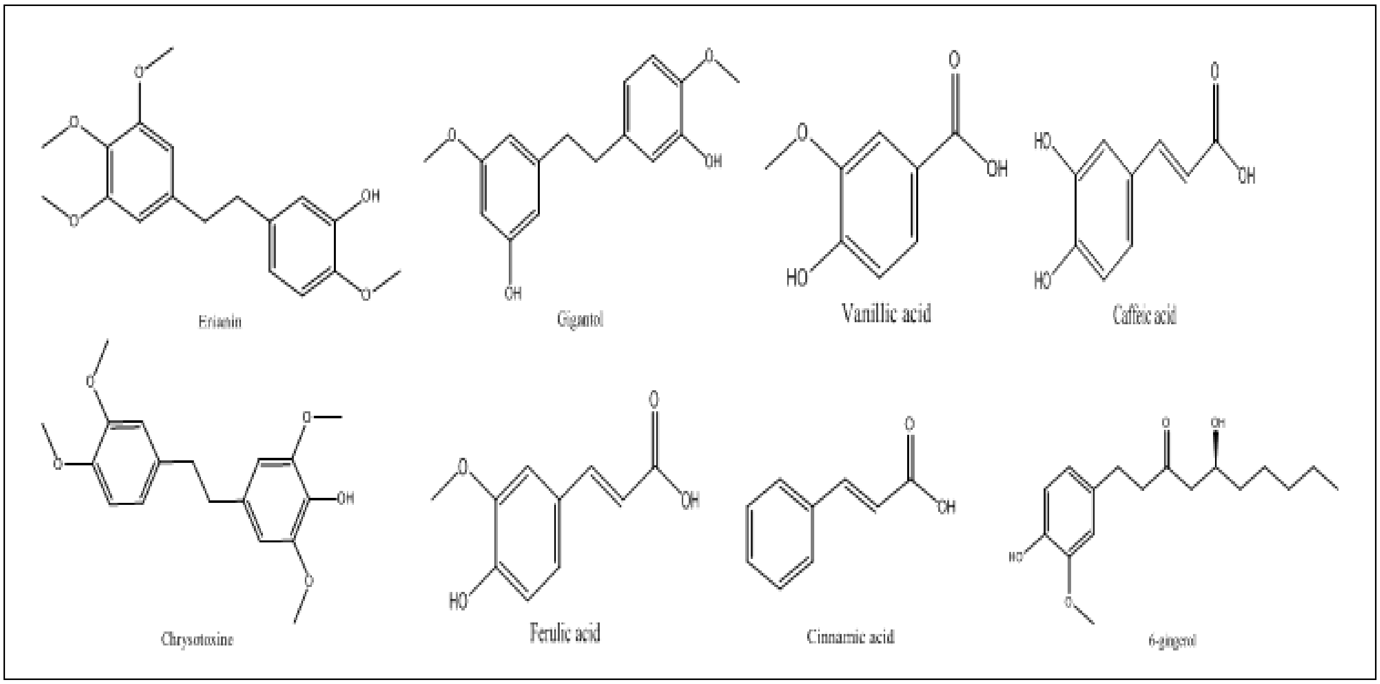
FLAVANONOLS **PHENOLIC COMPOUNDS** **ISOTHIOCYANATES**



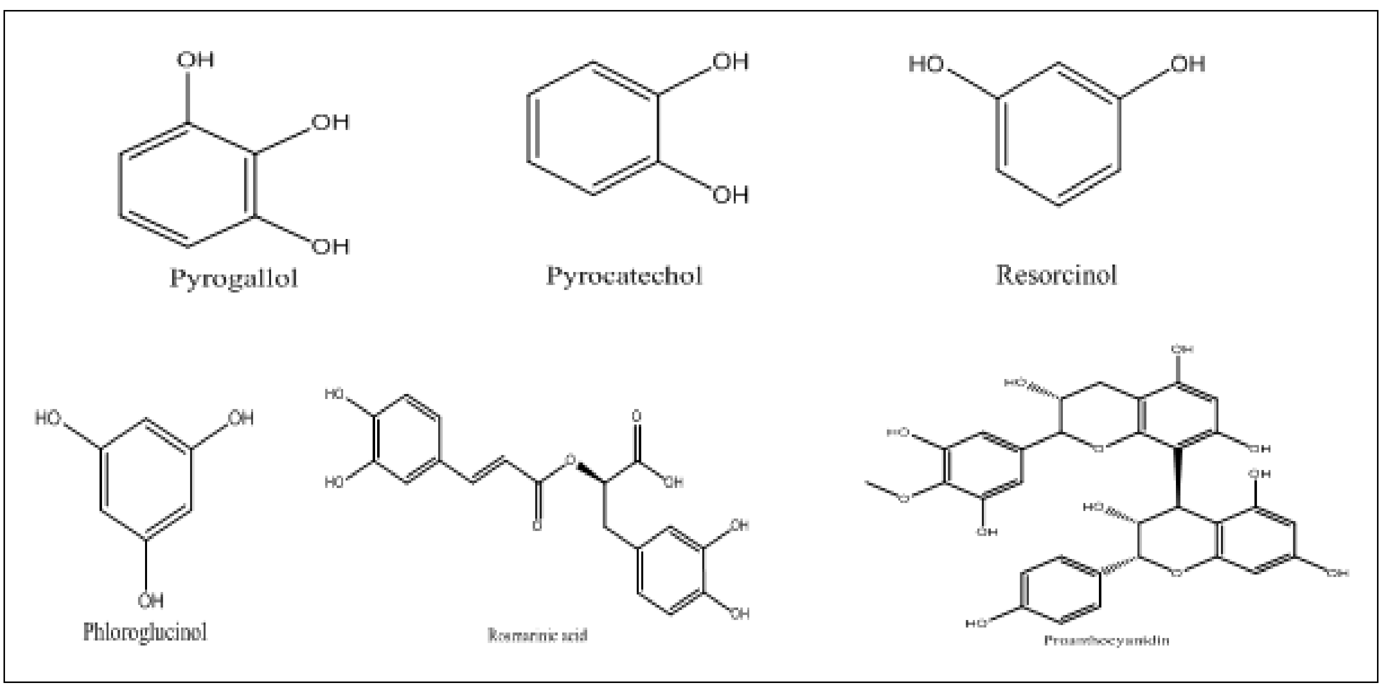
STILBENOIDS



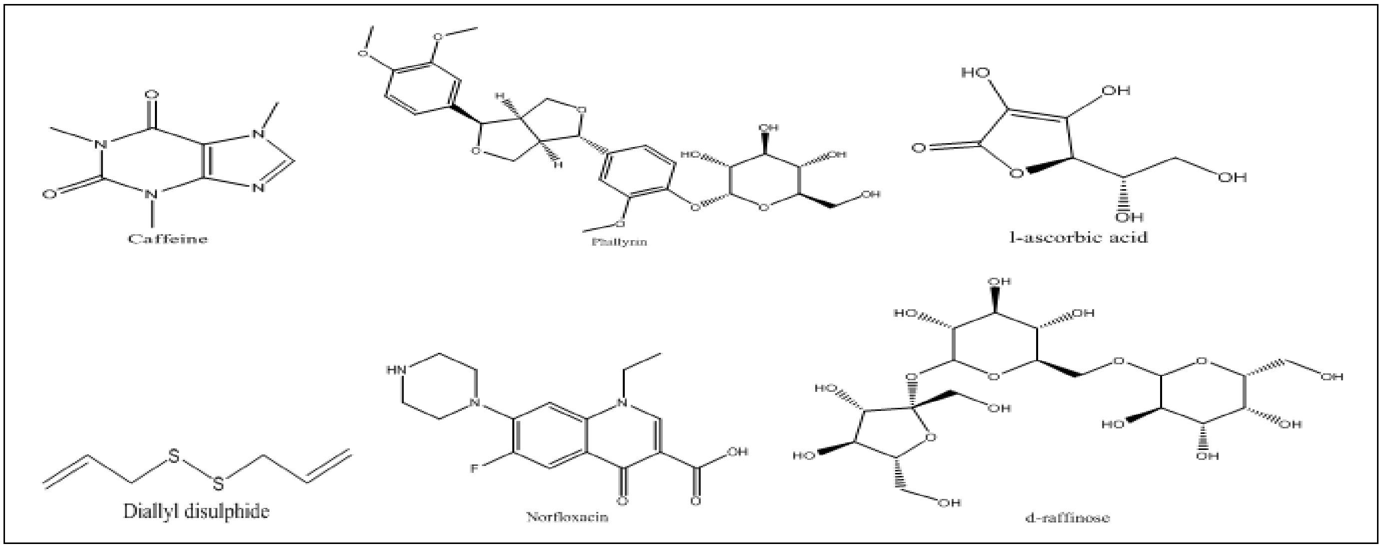
TERPENOIDS **SESQUITERPENES** **PHENANTHEROIDS**



AROMATICS BIS-BENZYL COMPOUNDS/BENZOIC ACID DERIVATIVES



POLYPHENOLS / PHENOLICS



OTHERS

CHART 3: STRUCTURE OF PHYTOCHEMICALS TESTED AGAINST *PSEUDOMONAS AERUGINOSA*

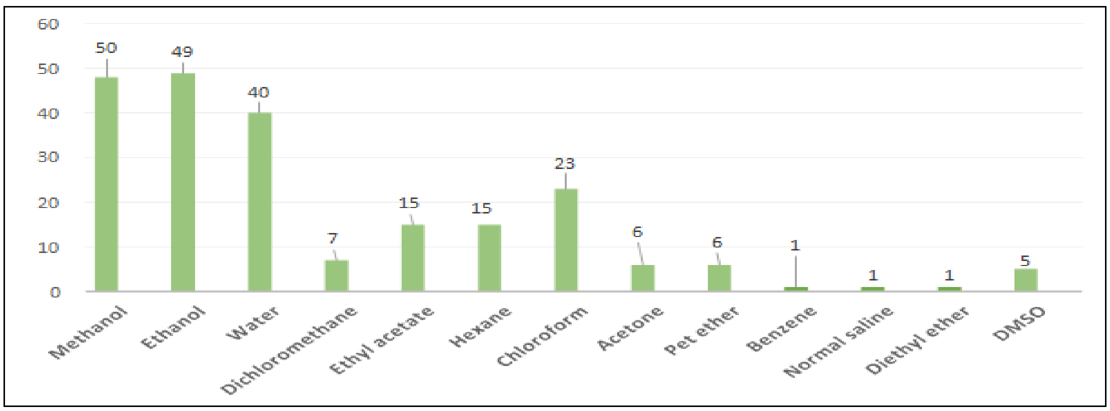


FIG. 4: VARIOUS SOLVENTS USED FOR PLANT EXTRACTION FOR ANTI-QUORUM STUDIES AGAINST *PSEUDOMONAS AERUGINOSA*

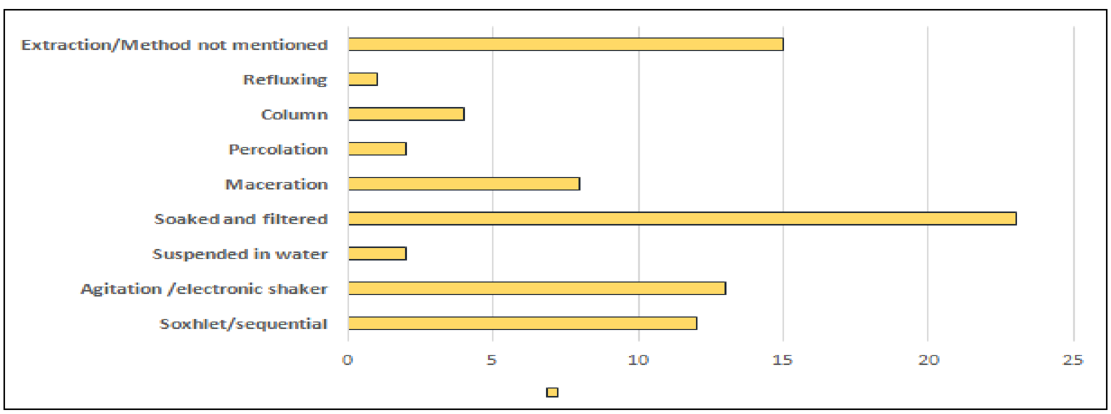


FIG. 5: DIFFERENT EXTRACTION METHODS USED FOR ANTI-QUORUM STUDIES AGAINST *PSEUDOMONAS AERUGINOSA*

Fig. 1 shows the comparison of anti-quorum sensing activity of various plant families against *Pseudomonas aeruginosa*. **Fig. 2** gives details of various plant parts used for anti-quorum sensing. Chart 3 represents the structures of phytochemical compounds tested against *P. aeruginosa*. Though various solvents are used for plant extraction for anti-quorum studies against *Pseudomonas aeruginosa* polar solvents are mostly used, and the polar extracts show good inhibitory activity **Fig. 4**. Plant materials tested for quorum sensing have been extracted by soaking and soxhlet extraction methods predominantly **Fig. 5**.

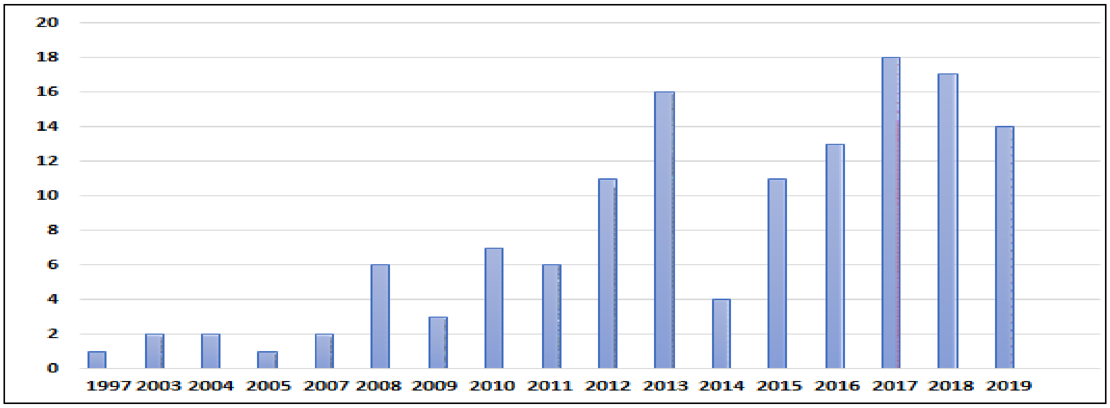


FIG. 6: PROGRESS ON ANTI-QUORUM STUDIES AGAINST *PSEUDOMONAS AERUGINOSA*

In the last one decade the number of reports on quorum sensing with medicinal plants has increased **Fig. 6**.

CONCLUSION: Traditional medicinal plants have been proved for their potential anti-quorum sensing activities against *Pseudomonas aeruginosa*. Polar extracts of plants are found to have significant activity when compared to other solvents.

Various types of phytochemicals extracted from these medicinal plants, especially flavonoids compounds are proved to be effective in down regulating quorum sensing in *Pseudomonas aeruginosa*. Plant extracts showing potential anti-quorum sensing activity with low MIC values are *Psidium guajava*, *Cassia alata*, *Camellia nitidissima*, *Anogeissus leiocarpus*, *Parkia javanica*, *Terminallia catappa*, *Neppenthes alata*, *Brassia oleraceae*, *Plantago asiatica*, *Terminallia bellerica*, *Quercus infectoria*, *Pistacia atlantica* and *Laserpitium ochridanum*. Since many of the modern-day medicines are of plant origin, these plant extracts may be further explored to develop as a potential alternative to reduce the misuse and overuse of antibiotics on human and animal health.

From among the tested compounds cinnamon oil showed the lowest MIC value (0.0001 mg/ml) followed by norfloxacin (0.00025 mg/ml), chrysin (0.025 mg/ml) and curcumin (0.030 mg/ml). Phytochemistry, through the simultaneous use of inhibitors for different targets / QS schemes, could also be of tremendous benefit in the fight against multiantibiotic bacterial diseases.

FUTURE PERSPECTIVES: With the remarkable technical advances in medicinal chemistry, molecular entities, especially of plant origin, which have not been investigated till date can be analyzed for anti-quorum sensing activity. Based on the potency of such compounds and their derivatives, future assessment can be performed through pre-clinical and clinical trials. In order to mitigate misuse and overuse of antibiotics on human health and the environment, this active area will require a great deal of focus. It is important to note, that QS inhibitors especially from plant sources are most likely to be beneficial when co-administered with conventional antibiotics as adjuvants rather than as standalone therapeutic agents.

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