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*Review*

# Elucidating the effect of anti-biofilm activity of bioactive compounds extracted from plants

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Biofilms are dense population of sessile bacterial cells that adhere to the surface, forming a matrix composed of exopolysaccharide, proteins and DNA. This matrix is termed as extracellular polymeric substance and provides stability to the cells adhering to it to form biofilms. It also provides nutrients and thus helps in the pathogenesis of biofilm-associated infections and resistance. Biofilms promote bacterial persistence by resisting host immune responses and antibiotic treatment. Antibiotics are rendered ineffective when biofilms form due to their relative impermeability, the variable physiological status of microorganisms, and subpopulations of persistent strains. Another factor that results in the development of antibiotic resistance within the biofilm is the adaptations that take place within the genes present in the cells dwelling within the biofilm. These adaptations decrease the sensitivity of the bacterial cells toward the antibiotics and develop resistance. Hence, an alternative antimicrobial strategy of making use of plant-based products has been observed to be useful to cure various ailments, as compared to conventional therapy. In this review, we have listed the various biofilm-forming bacteria and the bioactive compounds being produced from the aerial parts of plants having antibiofilm activity and evaluated them against different biofilm-producing bacterial strains.

**Keywords.** Antibiofilm; antimicrobial; bioactive; biofilm

## 1. Introduction

Biofilms formed by bacteria are defined as an adherent group of sessile communities of microorganisms surrounded by a matrix of extracellular polymeric substance (EPS), which attach themselves to a living or an inert surface (Baker and Banfield 2003). The biofilm attaches to abiotic surfaces, epithelia of multicellular organisms and interfaces of air and water (Druschel *et al.* 2004). The adhesion of bacteria to a surface is an essential step and is required for the bacteria to arrange themselves favorably with the environment. The microorganisms dwelling within the biofilm often develop not only antibiotic resistance but also resistance against common disinfectants and antiseptics that are regularly used. The development of resistance within the biofilm is a combined effect of coordinated gene expression and development of bacterial communication by quorum sensing (QS) (Anderl *et al.* 2000). The development of antibiotic resistance is the major cause of development of pathogenicity. Glycocalyx is one of the important components that helps in the formation of biofilms. The attachment of the sessile group of cells with the solid surface is mediated by the presence of hydrogen bonds, electrostatic forces and van der Waals forces of interaction within the biofilm (Peña *et al.* 2011). The resistance against antibiotics and antimicrobial agents is provided by components like polysaccharides and glycoproteins present within the matrix of the glycocalyx. The matrix prevents the transportation of the bactericidal agents up to the cells and thus prevents the cells from dying. The adsorption sites present within the matrix have the exoenzymes, which increase the resistivity of the cells toward the antibacterial agents (Hoyle *et al.* 1990; Arciola *et al.* 2012). Resistance of bacteria to multiple drugs has a genetic basis that has been thoroughly studied in the past few decades. These multidrug resistance (MDR) genes can help in the production of certain proteins or enzymes that can directly interfere with the drug molecules and degrade them or can activate certain pathways that may eventually bring about prevention of the antibiotic activity in MDR bacteria (Hiroshi 2009). These adaptations decrease the sensitivity of the bacterial cells toward the antibiotics and they develop resistance. The MDR of a bacterial cell is developed by multiple antibiotic-resistance operons that act as global regulators for the development of resistance. Another unique property of bacterial cells is that they

possess several repairing enzymes and exhibit oxidizing stress response (Greenberg and Demple 1988; Farr and Kogoma 1991).

There are various types of drug resistances depending upon the function of genetic products and the type of drug molecules. The resistance that is being observed in bacteria due to multiple exposures to a specific compound is known as secondary resistance (also called 'acquired resistance'). This secondary resistance can be achieved by various factors. It has been found that as a genetic product, β-lactamase that is present at the EPS matrix can hydrolyze the ester or amide bonds of antibiotics such as penicillin, amoxicillin etc. (Tanwar *et al.* 2014). Thus it causes structural modification to the drug molecule, ultimately leading to decreased penetration to the biofilm (Hall and Mah 2017).

Another mechanism of drug resistance can be described as the presence of extracellular DNA (eDNA). eDNA, being an anionic macromolecule, may cause a decrease in ionic concentration by the chelation of cations such as $Mg^{2+}$, causing significant alterations of the extracellular microenvironment, thus inhibiting drug activity. Sometimes it can induce synthesis of spermidine that helps in maintaining cell membrane integration (Hall and Mah 2017). Even over-expression of drug target enzymes may affect certain pathways in such a way that an alternate target molecule is created, which interferes with some other protein synthesis (Tanwar *et al.* 2014). Enhanced activity of various efflux pump genes due to some mutation may help in the extrusion of the antibiotics from the cell (May *et al.* 2009). Table 1 describes the genes from various bacterial species that are resistant to antibiotics and their mechanism of action.

Microbial biofilms possess various positive aspects that are a boon to our society. The biofilm comprises EPS that contains carbohydrates, proteins, fats and nucleic acids (Berlanga and Guerrero 2016). These compounds have various biotechnological utilities and are also used in cosmetics, food and pharmaceutical industries. One such application is the development of surfactants from the microbes dwelling within the biofilm. Biosurfactants find wide applications in commercial industries as agents for emulsion, wetting, foaming and phase dispersion (Fariq and Saeed 2016). They usually have lower toxicity and higher biodegradability compared with their synthetic chemical counterparts. For example, *Pseudomonas aeruginosa* produces extracellular secondary metabolites with surfactant-like properties known as rhamnolipids (Lequette and Greenberg 2005; Dusane *et al.* 2010). Biofilms are also used for the production of various chemicals such as ethanol and lactic acid at an industrial scale by the process of solid-state fermentation. The advantage of this technique is that it concentrates the enzymes associated with the cells at the biofilm–surface interface to increase the reaction rate. The layers of organisms associated with the biofilm cause easier conversion of complex substrates to simpler monomer compounds that helps in easier delignification and saccharification. The combined effect of solid-state fermentation and the association of biofilms has made the processing of biofuels much easier and faster (Doelle *et al.* 1992). Biofilms are very useful in processes such as waste water treatment, bioremediation and production of biofuels (Wang and Chen 2009). The classical method of the formation of biofuels involves various processes that become uneconomical; hence the use of microbial biofilms for the production of biofuels has made the process easier, faster and economical (Hahn-Hagerdal *et al.* 2006). Biofilms produced by various nitrifying bacteria are also used in waste water treatment. They can degrade different contaminants by mechanisms like biodegradation, biosorption, bioaccumulation and biomineralization and help in reducing toxic nitrite compounds (Shama and Iffat 2016). Bacterial biofilms from *Alcanivorax*, *Marinobacter*, *Pseudomonas* and *Acinetobacter* can effectively degrade hydrocarbons that provide us an innovative way to deal with oil spills in the oceans (Bayat *et al.* 2015). There are some bacterial biofilms that are useful to humans and other living organisms. For example, probiotic bacterial biofilm present mainly in the small and large intestine can help in strengthening our immune system and in digestion of food. *Streptococcus thermophiles* can break down the milk protein casein, thereby preventing allergies. It also promotes the growth of healthy tissues in the small intestine and can be used in cancer treatment (Whitford *et al.* 2009). Some bacterial species such as *Pediococcus acidilactici*, *Bacillus laterosporus*, *Lactobacillus* sp. etc. help in neutralizing toxins, balancing blood sugar, supporting digestion and boosting immunity (Ferguson *et al.* 2010; Amara and Shibl 2015).

Although biofilms have beneficiary effect, their ill effects are fatal, as they develop antimicrobial resistance. Biofilms may originate on indwelling medical devices from the skin of patients or healthcare personalities, tap water to which the devices are exposed and other environmental sources. Sometimes during the surgical implantation of prosthetic heart valves, tissue damage occurs which leads to the accumulation of platelets and fibrins, allowing for a greater possibility of formation of biofilms (Costerton *et al.* 1999). Some of the commonly isolated bacteria found on all venous catheters are, for example, *Staphylococcus epidermidis, Candida albicans, Staphylococcus aureus, P. aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis,* and *Proteus mirabilis*. The high pH conditions prevailing at biofilm–urine interface lead to precipitation of minerals such as hydroxyapatite and struvites, thereby completely blocking the inner lumen (Kokare *et al.* 2009).

Knowledge of antibiotics and antimicrobial agents is extensively used in today's medical treatments. Research studies have proved that antibiotic treatment can only eliminate planktonic forms of bacteria but the sessile forms develop resistance toward antibiotics and keep on propagating inside the biofilm (Costerton *et al.* 1999). Biofilms promote bacterial persistence by resisting host immune responses and antibiotic treatment (Raad *et al.* 1999). The development of the extra polysaccharide matrix causes slow

**Table 1.** Comparative analysis of genes from various bacterial species that are resistant to antibiotics and their mechanism of action

| Sl no. | Genes | Bacterial species | Resistant to antibiotics | Mechanism of action | References |
|---|---|---|---|---|---|
| 1 | brlR | *Pseudomonas aeruginosa* | Tobramycin, norfloxacin, trimethoprim, tetracycline, kanamycin, chloramphenicol | Upregulation of multidrug efflux pumps | Gupta *et al.* (2014), Chambers *et al.* (2014) |
| 2 | bla Genes | *E. coli, K. pneumoniae, Haemophilus influenza, P. aeruginosa, S. aureus* and *Neisseria gonorrhoeae* | Penicillin and its derivatives | Inhibits the drug by hydrolyzing it | Ehmann *et al.* (2013) |
| 3 | cat Gene | *S. aureus, E. coli, K. pneumoniae* | Chloramphenicols | Acylates the drug inhibiting the binding to the target | Schwarz *et al.* (2004) |
| 4 | dltABCD | *Streptococcus mutans* | Gentamicin | Decrease in the negative charge of the cell wall | Nilsson *et al.* (2016) |
| 5 | epaI | *Enterococcus faecalis* | Daptomycin | Unknown | Dale *et al.* (2015) |
| 6 | epaOX | *Enterococcus faecalis* | Gentamicin | Maintenance of cell wall integrity | Dale *et al.* (2015) |
| 7 | erm | *Streptococcus pyogenes, Streptococcus pneumoniae, E. coli* | Erythromycin, clarithromycin, azithromycin | Post-transcriptional methylation of an adenine residue in 23S rRNA | Mataseje *et al.* (2016) |
| 8 | exaA, pqqC, erbR, | *Pseudomonas aeruginosa* | Tobramycin | Efflux of antibiotics out of the cell | Beaudoin *et al.* (2012) |
| 9 | fsrA, fsrC | *Enterococcus faecalis* | Gentamicin, daptomycin, linezolid | Unknown – likely regulation of gelE expression | Dale *et al.* (2015) |
| 10 | gelE | *Enterococcus faecalis* | Gentamicin, daptomycin, linezolid | Unknown – perhaps promotion of extracellular DNA release? | Dale *et al.* (2015) |
| 11 | ndvB | *Pseudomonas aeruginosa* | Tobramycin, gentamicin, ciprofloxacin | Sequestration of antibiotics, upregulation of ethanol oxidation genes | Mah *et al.* (2003), Sadovskaya *et al.* (2010), Beaudoin *et al.* (2012) |
| 12 | PA0756-0757, PA2070, PA5033, psl | *Pseudomonas aeruginosa* | Tobramycin, gentamicin | Unknown | Zhang *et al.* (2013) |
| 13 | pelABCDEFG | *Pseudomonas aeruginosa* | Tobramycin, gentamicin | Unknown – possible link with eDNA? | Colvin *et al.* (2011) |
| 14 | Qnr genes | *Klebsiella pneumoniae, Enterobacter cloacae, E. coli* | Fluoroquinolones | Qnr proteins bind to fluoroquinolone and alters the activity | Guo *et al.* (2010) |
| 15 | rapA | *Pseudomonas aeruginosa* | Penicillin G, norfloxacin, chloramphenicol, gentamicin | Upregulation of YhcQ and of exopolysaccharide synthesis | Lynch *et al.* (2007) |
| 16 | relA, spoT | *Pseudomonas aeruginosa* | Ofloxacin, meropenem, colistin, gentamicin | Upregulate antioxidant defences and downregulate pro-oxidants | Nguyen *et al.* (2011), Khakimova *et al.* (2013) |
| 17 | sagS | *Pseudomonas aeruginosa* | Tobramycin, norfloxacin | Activation of BrlR by promoting increased c-di-GMP levels | Petrova and Sauer (2011), Gupta *et al.* (2014) |
| 18 | sul1/2 Genes | *Salmonella enterica* | Sulfonamides | Altered production of dihydropteroate synthase that is found mostly in class 1 integron plasmids | Johnson *et al.* (2007) |
| 19 | tssC1, hcp1 | *Pseudomonas aeruginosa* | Tobramycin, gentamicin, ciprofloxacin | Unknown | Zhang *et al.* (2011) |
| 20 | yafQ | *Pseudomonas aeruginosa* | Tobramycin, cefazolin | Persister cell formation | Harrison *et al.* (2009) |

or zero diffusion of antibiotic compounds in the biofilm. The altered microenvironment causes a concentration gradient of the metabolites, leading to regions of slow or non-growing bacteria. The fluctuations in the microenvironment such as changes in temperature and nutrient supply, oxidative stress, low water availability and starvation activate the adaptive stress responses in the bacteria. This in turn leads to transformation of some of the bacterial cells such that they enter into a highly protected spore-like state known as persisters. It is the presence of persisters inside the biofilm that is responsible for the observed antibiotic resistance (Stewart 2002) and prevents the conventional approach of medicines (Chadha 2014). Thus, biofilms are considered as a target for pharmacological development. Recent studies have shown that natural agents having plant secondary metabolites can disrupt biofilms. Hence, researchers are focusing on herbal treatments to fight against biofilms. Moreover, plant extracts are considered to be the safest as they are naturally derived and do not harm the host tissues surrounding the biofilms while acting upon them.

### 1.1 *Steps of formation of biofilm*

The biofilm formation starts with the transport of planktonic cells from the bulk liquid to the surface, leading to cell aggregation. This causes increase in the concentration of chemical substances (production of cell–cell signaling molecules) leading to genetic changes within the cells, resulting in tight binding of cells to the surface and neighboring cells. The microcolonies thus developed produce a thick extracellular matrix composed of exopolysaccharide, protein, eDNA and other polymers that form a protective physical barrier around the bacteria. This allows them to grow into a mature biofilm of complex communities that are capable of QS (Chen *et al.* 2004; Hornby and Nickerson 2004).

Figure 1 shows the various steps in biofilm formation. It involves the irreversible adsorption of bacterial cells on the surface, production of cell signaling molecules by the biofilm-forming cells, transport of substrates to or within the biofilm, substrate metabolism by the biofilm-forming cells and transport of products out of the biofilm.; This is accompanied by cell growth, replication and EPS production.

QS is the ability of the bacterial cells to sense bacterial density by cell-to-cell signaling using autoinducers. Autoinducers are signaling molecules that are produced in response to changes in cell-population density. The detection of signal molecules by bacteria acts as a stimulation that leads to altered gene expression once the minimal threshold is reached (Davies *et al.* 1998). These autoinducers cause aggregation of the biofilm-forming cells with one another by the secretion of EPSs. QS is the mechanism by which both Gram-positive and Gram-negative bacterial cells develop biofilms by producing signaling molecules such as small peptides, acyl-homoserine lactones (AHL) and quinolones. In Gram-negative bacteria, the bacterial systems employ the autoinducer homoserine lactones (HSL) synthesized by genes *LuxI* homologue and *LuxR* homologue that encode a transcriptional activator protein that detects the cognate HSL inducing the appropriate phenotype. In contrast, Gram-positive bacteria use the secreted peptide as the autoinducer for QS. Different bacteria have different mechanisms for QS, for example, *Bacillus subtilis* and *Streptococcus pneumoniae* use QS to develop bacterial competence. *S. aureus* regulates virulence while *E. faecalis* employs QS to regulate conjugation (Bassler 1999; Gera and Srivastava 2006). In bacteria, the QS systems have been divided into three classes: (1) LuxI/LuxR-type QS in Gram-negative bacteria that use AHL as signal molecules, (2) oligopeptide-two-component type QS in Gram-positive bacteria that use small peptides as signal molecules and (3) LuxS-encoded autoinducers (AI)-2 QS in both Gram-positive and Gram-negative bacteria. This technique is used by bacterial pathogens to regulate the genes that promote defense, invasion and spread of the pathogenicity. Thus, signaling molecule (AHLs)-mediated QS is responsible for biofilm formation and hence for bacterial pathogenicity.

There are few reports that suggest lack of signaling molecules in biofilm formation. For example, production of biofilm and AHL in *P. aeruginosa* isolates was checked in the presence of sub-inhibitory concentration of antibiotics (Kilinc *et al.* 2018). It was found that biofilm formation extended in species with no synthesis of AHL signaling molecules, leading to the hypothesis of the presence of a different signaling molecule besides AHL. In another study, *Burkholderia cepacia* complex from several genomic species of *B. cepacia* showed nutrient media depended biofilm formation and HSL synthesis. It was found that HSL synthesis and biofilm formation were linked together in Luria broth. However, the two processes appeared to be independent in basal salt media, with few strains producing the highest amounts of HSL and the rest producing most abundant biofilms (Conway *et al.* 2002). Another study emphasized on the biofilm formation by exogenous QS signaling molecule AHL in the marine bacterium *Pseudoalteromonas ulvae* TC14. It is seen that TC14 does not produce intrinsic AHLs. However, TC14 is capable of

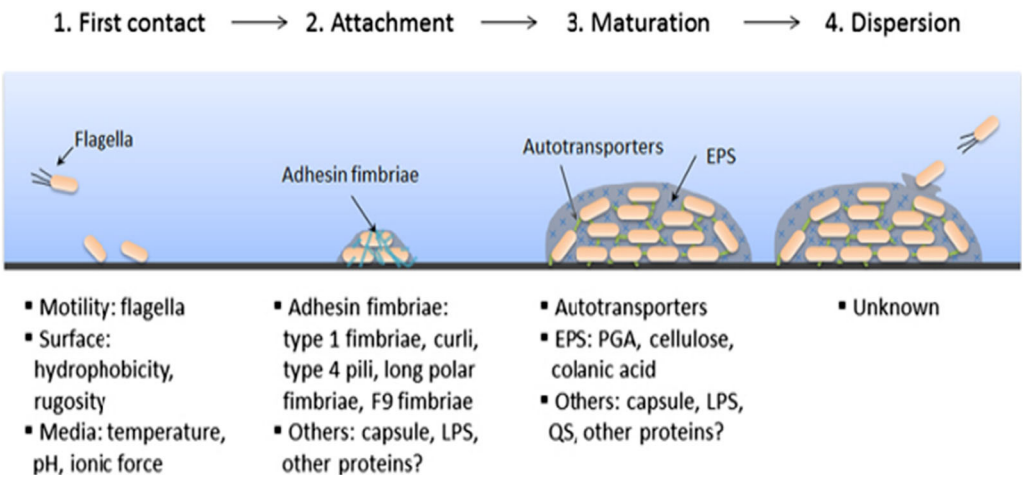


**Figure 1.** Steps of biofilm formation by bacterial cells (adapted from *Frontiers in Microbiology* 2014, 5(317):317).

detecting the presence of exogenous AHL in planktonic conditions due to the presence of the functional LuxR-type QS receptor system which in turn helps in biofilm formation (Aye *et al.* 2015). Thus, further experimental support is required to understand the pathway of biofilm formation.

### 1.2 *Antimicrobial resistance and phyto-therapy*

Antimicrobial resistance is one of the biggest problems threatening global public health as it arises due to microbial adaptation to antibiotics used in areas like animal food, medicines and disinfectants in hospitals, farms and households. The exploration of alternative therapies is essential nowadays as microorganisms are developing resistance against antibiotics. Resistance allows microorganisms to grow in toxic conditions. The evolution of pathogen resistance has reduced the effectiveness of many antimicrobial drugs. Thus, the development of drugs from natural sources is of major interest.

We came across antibiofilm compounds that prevents the implantation of sessile group of bacterial cells on the surface causing inhibition to biofilm formation thus preventing biofilm associated infection. To date, majority of the existing anti-biofilm agents are nonbiocidal (Miquel *et al.* 2016). However, some bactericidal molecules can be considered as anti-biofilm agents. In this review, we will focus on naturally derived compounds of plants (plant extracts) having therapeutic activities and their effects on biofilm formation.

### 1.3 *Cytotoxicity study of plant-derived compounds*

Microbial adaptation to antibiotic substances has led to an intense search for new antimicrobial agents, especially from plants. The determination of cytotoxicity of plant extracts is an important aspect for the bioactive compound to be used at a commercial level. The viability of the cells is determined by the reduction of the MTT dye (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) with the help of dehydrogenase enzymes of active cells that convert the water-soluble yellow dye to purple formazon crystals (Mosmann 1983; Carmichael *et al.* 1987; Morgan 1998). Various cytotoxicity studies are performed using different types of plant extracts using the MTT-assay test. The ethanol extract of *Terminalia fagifolia* stem bark showed antibacterial and antibiofilm activities. Additionally, this extract was also found to be cytotoxic in the cell line NIH/3T3 and has potential antitumoral activity in the human breast cancer cell line MCF-7 (Araujo *et al.* 2015). Essential oils extracted from *Agastache rugosa* showed effective antibiofilm and antitumor activities. Cell viability assay (MTT) against gastric cancer cell line SGC-7901 induced by essential oils of *A. rugosa* showed inhibited cytotoxicity (Haiyan *et al.* 2016). Methanolic extracts of *Hakea sericea* Schrader fruits decrease the viability of human breast adenocarcinoma cells (MCF-7), thus confirming its antimicrobial, antibiofilm and cytotoxic activities (Luís *et al.* 2014).

### 1.4 *Bioactive compounds*

The antibiofilm activity of plant extracts is due to the presence of bioactive compounds. These are plant secondary metabolites that are extra nutritional constituents that are present in very small amounts in plants that have the ability to influence the physiological and cellular activities in animals and humans that consume them. A wide range of classification of bioactive compounds is possible depending upon their various functions. Table 2 shows some of the major classes of bioactive compounds.

*Essential oils* are the concentrated volatile compounds found in many plants, which are hydrophobic in nature. Recently, these are widely being used along with nanoparticles and antibiotics to fight against the formation of biofilms (Algburi *et al.* 2017).

*Glycosidic* linkages are found within the exopolysaccharide of biofilms (Fleming *et al.* 2017). The herbal extracts contain glycoside hydrolase enzyme that helps in degrading the polysaccharide chain by breaking them into smaller subunits or monomers which in turn will help in reducing the biofilm. The α-amylase can cleave the α-1,4-straight-chain linkage and β-1,4 bond and β-1,3 galactosidase can hydrolyze the β-1,3 linkage degrading the external coating (Fleming *et al.* 2017). *Anthocyanidins* are the major components extracted from cranberries and are widely used for the treatment of bladder and kidney ailments. *Escherichia coli* adhere to the urinary tract epithelial cells forming biofilms whose pathogenesis causes urinary tract infections. Proanthocyanidins (PACs) resist the formation of biofilms by preventing intercellular adhesion to urinary tract lining or by decreasing uroepithelial cell attachment (Mary Ann Liebert 2009).

*Tannins* are the groups of water-soluble polyphenolic compounds that serve as defense mechanisms for plants. They contain the protein immunodominant staphylococcal antigen A (IsaA). IsaA acts as an important inhibitor of biofilms as it is a putative lytic transglycosylase that can breakdown the β-1,4 glycosidic bond between *N*-acetylglucosamine and *N*-acetylmuramic acid (Rabin *et al.* 2015). Thus, tannins help in inhibiting biofilm formation by decreasing the surface area of the peptidoglycan layer and increasing the penetration of the applied antibiotic (Payne *et al.* 2013).

*Alkaloids* are a class of secondary metabolites present in plants. The action of different alkaloids is different for different microorganisms: the action of 1,3,4-oxadiazole inhibits the production of the toxin called pyocyanin and QS signal precursor HHQ in *P. aeruginosa* (Morkunas *et al.* 2016); the action of 7-hydroxyindoloe alters the virulence gene expression and abolishes swarming motility (Lee *et al.* 2009); and solenopsin A inhibits virulence gene transcription and the production of the destructive enzyme elastase B

**Table 2.** Major classes of bioactive compounds extracted from plants

| Sl. No. | Name | Class | Bioactive compound | Plant parts used | Activity | Medicinal use | Organisms used | References |
|---|---|---|---|---|---|---|---|---|
| 1 | *Aegle armelos* | *Carotenoids, phenolics,* | *Sinapic acid* | Leaves | Anti-hyperlipidaemic, antibacterial, antioxidant, anti-biofilm | Throat infections, cold, intestinal ailments, fertility, chest congestion, fish poison, child birth | *Salmonella typhi, Escherichia coli, Pseudomonas aeruginosa* | Rejiniemon *et al.* (2014), Govinda (2011) |
| 2 | *Aervalanata* | *Methanolic* | *Alkaloid* | Leaves | Antioxidant, anti-helmentic, anti-inflammatory, diuretic | Jaundice, dyspepsia, pneumonia | *Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Proteus vulgaris* | Abinaya *et al.* (2016), Anita and Retna (2013) |
| 3 | *Aesculus hippocastanum* | *Flavonoids* | *Quercetin and kaempfero* | Bark, seed and leaf | Antibiofilm, anti-aging | Varicose veins, hemorrhoids, and swollen veins | *Staphylococcus aureus, Staphylococcus epidermidis* | Antoniuk (1992), Artini *et al.* (2012) |
| 4 | *Agrimoniaeupatoria* | *Phenolic* | *Feruilic acid* | Flowers | Antidiabetics, anticancer, anti-biofilm, anti-bacterial | Urinary tract disorder | *Pseudomonas aeruginosa, Proteus mirabilis* | Muruzovic *et al.* (2016), Sytara *et al.* (2016) |
| 5 | *Allium sativum* | *Flavonoids* | *(Thiosulfinates and ajoene* | Leaf | Anti-inflammatory activities, antibiofilm | Common cold, malaria, lung tuberculosis, hypertension | *Escherichia coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus cereus* | Mohsenipour and Hassanshahian (2015), Hughes *et al.* (1989) |
| 6 | *Anadenantheracolubrina* | *Terpinoids* | *Linalool* | Branches, stems bark | Antimicrobial, anti-proliferative, anti-biofilm | Inflammation, throat, lung and kidney problems, chest inflammation | *S. epidermidis, Pseudomonas aeruginosa* | Trentin *et al.* (2014), Maria and Pedone-Bonfim (2013) |
| 7 | *Andrographis paniculata* | *Essential oils* | *Citral* | Leaf | Anti-inflammatory activities, antibiofilm | Toothaches, common cold, digestive problems, oral infection and wound heal | *Pseudomonas aeruginosa* | Murugan *et al.* (2011) |
| *8* | *Arctiumlappa* | *Essential oils* | *p-cymene, Carvone* | Leaf | Antimicrobial, antioxidant, anti-biofilm. | Diuretic, diaphoretic, blood purifying agent. | *Staphylococcus aureus* | Tang *et al.* (2014), Chan *et al.* (2011), Tonea *et al.* (2016) |
| 9 | *Artocarpus lakoocha* | *Flavonoids, stibinoids* | *Cycloheterophyllin, triterpenic; resveratrol* | Bark | Anti-inflammatory, anti-cancer, anti-HIV properties | Wound, skin lesion | *Candida albicans, Candida tropicalis, Candida dubliniensi* | Sukunlaya *et al.* (2014), Hossain *et al.* (2016) |
| 10 | *Azadirachta indica* | *Essential oils* | *Oleic acid (31.3%), hexadecanoic acid (14.2%)* | Leaves | Antibacterial, anthelminthic | Various ailments, act as contraceptive and sedative agent | *Escherichia coli, Pseudomonas aeruginosa* | Namsivayam and Roy (2013), Kusum *et al.* (2013) |
| 11 | *Buchananialanzan* | *Ethanolic extract, flavonoids* | *5-Hydroxy-7,8-dimethoxyflavone* | Root | Anti-inflammatory, antibacterial, antioxidant activities | Cardiotonic, astringent, glandular swelling, cyclophosphamide induce genotoxic | *Escherichia coli, Pseudomonas aeruginosa* | Pattnaik *et al.* (2013), Gonçalves *et al.* (2015) |
| 12 | *Calendula officinal* | *Flavonoids* | *Kaempferol-3-neohesperidoside* | Flowers | Antibacterial, anti-biofilm, antiedematous, antiseptic action, antioxidant, antispasmodic activities | Smallpox, jaundice, costiveness, ointment for wound | *Salmonella, Shigella dysenteriae, Shigella flexneri, Shigella sonnei* and *Escherichia coli* | Ghaima *et al.* (2013), Muley *et al.* (2000), Alexandrovich and Sharova (2007) |
| 13 | *Chamaemelumnobile* | *Flavonoids* | *Vanillic acid α-bisabol, α-bisabol oxides A and B, spathulenol and farnesene.* | Flowers | Antiseptic, anti-swarming activities, anti-inflammatory, anti-microbial | Malaria, peptic ulcer, wound healing | *Pseudomonas aeruginosa* | Kazemian *et al.* (2015), Deans (2003) |
| 14 | *Chelidoniummajus* | *Flavonoids* | Luteolin, Kaempferol glycosides | Flower, bark, root, aerial parts | Antimicrobial and antibiofilm effects | | *Staphylococcus aureus, S. epidermidis* | Maji *et al.* (2015) |
| 15 | *Chromolaenaodorata* | *Phenolic* | *Ferulic acid* | Leaves | Antibacterial, antioxidant, anti-biofilm activity | Cough, malaria | *Pseudomonas aeruginosa* | Yahya *et al.* (2014), Harlina *et al.* (2016) |
| 16 | *Coriandrum sativum* | *Essential oils* | Geraniol, menthol | Seed | Antibiofilm activity | Worms, pain in joints and rheumatism | *Staphylococcus aureus* | Bezalwar and Shuddhalwar (2013), Silva and Domingues (2015) |
| 17 | *Cymbopogon flexuosus* | *Essential oils* | *Neral, geranial, geraniol, limonene, citronellal, and β-myrcene* | Leaf | Anti-inflammatory activities, antibiofilm | Cosmetics, insecticides, digestive disorder. | *Staphylococcus aureus* | Avoseh *et al.* (2015), Schaneberg and Khan (2002) |

**Table 2** (continued)

| Sl. No. | Name | Class | Bioactive compound | Plant parts used | Activity | Medicinal use | Organisms used | References |
|---|---|---|---|---|---|---|---|---|
| 18 | *Euphorbia hirta* | *Flavonoids, terpenoids, phenols, essential oil* | *Citral, carvone* | Arial | Antihypertensive, anxiolytic, antimalarial, anti-inflammatory, anticancer activities | Bronchial, parasitotosis, amoebic dysentery, and respiratory ailments. | *Pseudomonas aeruginosa* | Perumal and Mahmud (2013), Nyeem *et al.* (2017) |
| 19 | *Ficussansibarica* | *Methanolic* | *Saponnin* | Fruits, leaves, stem barks | Antioxidant, antibacterial, antifungal, antidiabetics, anticancer, anti-inflammatory | Tuberculosis, diabetes malaria | *Escherichia coli, Staphylococcus aureus* | Awolola *et al.* (2014) |
| 20 | *Gymnemasylvestre* | *Essential oils* | *Cinnamic acid P-cymene* | leaves | Anti-biofilm, antibacterial activities | Blood sugar, lipid – lowering agent, ailments constipation, liver disease, contro, blood sugar | *Streptococcus pyogenes* | Dineshbabu *et al.* (2015) |
| 21 | *Hakea sericea* | *Phenolic* | *Ulmifolius, Hakea sericea, Cytisusmultiflorus, Crataegusmonogyna* | Aerial parts | Anti-bacterial, anti-biofilm and cytotoxicity activity | No medicinal uses | *Staphylococcus aureus* | Luís *et al.* (2014), Ranade *et al.* (2016) |
| 22 | *Helichrysumitalicum* | *Phenylpropanoids* | Methanol | Leaf | Inflammatory, anti-infection properties | Colds, skin, liver, gallbladder disorder, inflammation | *Pseudomonas aeruginosa* | D'Abrosca *et al.* (2013), Antunes *et al.* (2014) |
| 23 | *Herniariaglabra* | *Phenolic componds* | *Ellagic acid, α-terpineol* | Leaf | Anticonvulsant, astringent, antirheumatic activities | Respiratory problem, urinary tract infect | *Escherichia coli* | Wojnicz *et al.* (2012), Yordi *et al.* (2015) |
| 24 | *Hibiscus sabdariffa* | *Phenolic compounds* | *Ellagic acid, α-terpineol* | Leaves | Antibacterial, anti-biofilm, antioxidant, antihypertensive, anticancer | Mild laxative, cardiac diseases | *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella pneumonia* | Abbas *et al.* (2014), Puro *et al.* (2014), Formagio *et al.* (2015) |
| 25 | *Humulus lupulus* | *Prenylflavonoid's compound* | (+)-catechin | Hop cones | Biofilm, antibacterial, anti-inflammatory | Nervous tension, headache, indigestion, sedative. | *Staphylococcus aureus* | Rozalski *et al.* (2013), Koettar and Biendi (2010) |
| 26 | *Ibicella lutea* | *Phenolic* | *Sinapic acid* | Aerial parts | Anti-oxidant,anti-biofilm, anti-bacterial activity | Skin infection | *Proteus mirabilis* | Sosa and Zunino (2009) |
| 27 | *Kaempferia rotund* | *Essential oils* | *Thymol, Carvacrol* | Rhizomes | Antitumor, antiulcer, anti-inflammator | Heal wounds, cure stomach ailments, post-delivery care, blood clots | *Pseudomonas aeruginosa, Staphylococcus aureus* | Pratiwi *et al.* (2015), Atun *et al.* (2017) |
| 28 | *Lagenariasicerarit* | *Flavonoids, capsaicinoids and capsinoids* | *Quercetin-3-O-rutinoside* | Fruits, leaves | Antifungal, antioxidant, radio-protective | Immuno-suppressant, cardio-tonic, cardio protective, diuretic, nutritive agent, purgative, antidote force | *Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Streptococcus pnueumoniae, Streptococcus pyogenes* | Mutalib *et al.* (2015) |
| 29 | *Lavandula angustifolia* | *Phenolic compounds, essential oil* | *Ellagic acid, α-terpineol* | Essential oil | Antifungal activities, antibiofilm | | *Escherichia coli* | Budzynska *et al.* (2011), Hajhashemi *et al.* (2003) |
| 30 | *Leucas aspera* | *Methanolic* | *Coumaric acid* | Whole plant | Anti-inflammatory, antidiarrheal, antioxidant, antibacterial, hepatoprotective, anti-diabetic activity | Laxative, and diaphoretic, snake bite | *Staphylococcus aureus,* | Chew *et al.* (2012) |
| 31 | *Melaleuca alternifolia* | *Essential oils* | Terpinen-4-ol, terpinolene, α-terpinene, and α-terpineol | Leaves | Antimicrobial, antiseptic | | *Candida albicans* | Rasteiro *et al.* (2014) |
| 32 | *Melissa officinalis* | *Phenolic* | *Syringicacid, Gallic acid* | Essential oil | Antifungal, antimicrobial | Sleep disorder, spasmolytic, Alzheimer diseases | *Escherichia coli, Staphylococcus aureus* | Jalal *et al.* (2015) |
| 33 | *Mentha arvensis* | *Essential oils* | *Thymol* | Essential oil of leaf | Antibacterial, anti-biofilm activity | Indigestion, peptic ulcer, skin diseases | *Aggregatibacteractinomycetemcomitans* | Karicheri and Antony (2016) |

**Table 2** (continued)

| Sl. No. | Name | Class | Bioactive compound | Plant parts used | Activity | Medicinal use | Organisms used | References |
|---|---|---|---|---|---|---|---|---|
| 34 | *Mentha piperita* | *Peppermint Oil* | *Hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and propyl gallate (PG)* | Essential oil of leaf | Antibiofilm, antifungal | Toothpaste, digestive tablets | *Aggregatibacteractinomycetemcomitans, Candida albicans, Candida dubliniensis* | Sharafi *et al.* (2010), Saharkhiz *et al.* (2012) |
| 35 | *Murraya koenigii* | *Phenolic* | Protocatechuic acid | Leaves | Antidiabetics activities, cholesterol reducing property, phagocytic activities | Inflammation, itching, vomiting, chronic, tonic wound | *Pseudomonas aeruginosa* | Handral *et al.* (2012), Ganesh and Vital (2015), Nouman *et al.* (2015) |
| 36 | *Myracrodruonurundeuva* | *Methanolic* | *Alkaloid, terpinoid* | Leaves, steam, bark | Anti-inflammatory, anti-allergic, anti-biofilm | Inflammations, acne, pain, skin problems, allergy | *Staphylococcus epidermidis* | Trentin *et al.* (2014) |
| 37 | *Myroxylon peruiferum* | *Flavonoids* | *Luteolin-7-O-glycoside* | steam, bark, leaves | Antibiofilm, anti-bacterial activities | Asthma, cold, diarrhea, skin parasites, rheumatism and | *Staphylococcus epidermidis* | Goncalves *et al.* (2011) |
| 38 | *Ocimumtenuiflorumi* | *Phenolic acids* | *Protocatechuic acid, vanillic acid* | Leaves | Anti-carcinogenic properties, anti- genotoxic, neuroprotective,antibiofilm | Vomiting, flatulence, healing of peptic ulcer, coughs, colds inhibition | *Escherichia coli* | Namsivayam and Roy (2013) |
| 39 | Ourateablanchetian | Essential oils | Eugenol, Geranyl acetate | Branches, leaves | antimicrobial activities | Diarrhea, sprains, arthritic disorder | *Pseudomonas aeruginosa* | Carbonari *et al.* (2006), Trentin *et al.* (2011), Sasidharan *et al.* (2011) |
| 40 | *Ozaroa insignis* | *Phenolic* | Salicylic acid, gallic acid | Roots | Antibacterial, antimicrobial and cytotoxic | Primary medicinal use | | Fern (2014) |
| 41 | *Piper longum* | *Methanolic* | *Alkaloid, terpinoid* | Leaves | Antibiofilm, antibacterial, antioxidant activity | Malaria, asthma, cough, diabetes and heart problems | *Streptococcus pyogens* | Darsini *et al.* (2015) |
| 42 | *Pittosporum tetraspermum* | *Flavonoids, phenolic acids, carotenoids and vitamins C, E, A* | *Isorhamnetin, hesperidin, Iridoids, Pinene.* | Leaves | Anticancer, antibiofilm, antifungal, anti-microbial | Chronic bronchitis, rheumatism, skin diseases, cutaneous, leprosy | *Salmonella typhi, Pseudomonas aeruginosa* | Abdullah Al-Dhabi *et al.* (2015), De Queiroz *et al.* (2010) |
| 43 | *Pityrocarpamomoniliformis* | *Phenolic* | *Umbelliferone* | Leaves | Antibaacterial activities, antinociceptive | Healing process | *Staphylococcus epidermidis, Pseudomonas aeruginosa* | Silva *et al.* (2013), Mary and Banu (2015) |
| 44 | *Plectranthusamboinicus* | *Essential oil and carvacrol* | *P-cymene, Carvone* | Leaf | Antimicrobial, anti-inflammatory, antitumor, wound healing, anti-epileptic | Constipation, headache, fever | *Pseudomonas aeruginosa, Vibrio harvey* | Sasidharan *et al.* (2011), Sangam *et al.* (2010) |
| 45 | *Pongamiapinnata* | *Flavonoids* | *Xanthohumol, Pelargonidin chloride* | Leaves | Anti-inflammatory, antidiarrhoeal, antioxidant, anti-hyperammonemi, antiulcer | Antihelminthitic, gonorrhea, leprosy inflammation | *Streptococcus mutans* | Sangam *et al.* (2010) |
| 46 | *Rhodomyrtustomentosa* | *Phenolic* | *Vanillic acid* | Leaf | Antioxidant, antibacterial, antibiofilm, cancer-chemoprevention | Diarrhea, wound healing, urinary test infection | *Streptococcus pyogens* | Limsuwan and Voravuthikunchai (2008), Hazrulrizawati and Hamid (2017) |
| 47 | *Rosa canin* | *Phenolic compounds* | *Sinapic acid* | Leaf | Antimicrobial, anti-biofilm activities | Infections, inflammatory diseases, chronic pain, flu and alcoholic beverage | *Pseudomonas aeruginosa, Salmonella typhimurium* | Zivkovic *et al.* (2015), Ahmad (2016) |
| 48 | *Saliva triloba* | *Ethanolic* | *Volatile oil* | Leaves | Anti-inflammatory activities | Sexual transmitted, mental disorder, liver diseases, asth | *Staphylococcus aureus, Escherichia coli and Candida albicans* | Al-Bakri *et al.* (2010) |
| 49 | *Salvia officinallis* | *Phenolic* | Gallic acid | Aerial parts, leaves | Antibiofilm, anti-inflamatory | Digestive problems, Depression, memory loss, Alzheimer's disease | *P. aeruginosa* | Stojanović-Radić *et al.* (2016) |
| 50 | *Terminalia fagifolia* | *Flavonoids and triterpenes* | *Kahweol, Terpeneol* | Stem bark | Antibiofilm, antioxidant | Gastrointestinal disturbances, such as ulcer, gastritis | *Staphylococcus aureus, Staphylococcus epidermidis* | De Araujo *et al.* (2015) |
| 51 | *Tridaxprocumbens* | *Flavonoids* | *Kaempferol-3-neohesperidoside* | Leaves | Antibiofilm, antimicrobial, anti -inflamaatory | Antidiabetic, antiobesity, hair growth promotes, and insect repellent | *Escherichia coli* | Namsivayam and Roy (2013), Mundada and Shivhare (2010) |

**Table 2** (continued)

| Sl. No. | Name | Class | Bioactive compound | Plant parts used | Activity | Medicinal use | Organisms used | References |
|---|---|---|---|---|---|---|---|---|
| 52 | *Vaccinium vitis–idaea* | *Phenolic componds* | *Syringicacid,Gallic acid* | Leaf | Antibacterial, antioxidant, anticancer | Cyst, obesity, skin diseases, wounds, mycosis | *Escherichia coli* | Wojnicz *et al.* (2012), Sari (2006) |
| 53 | *Vinca minor* | *Phenolic* | *Ferulic acid, Salicylic acid* | Leaves | Anti-microbial, anti-inflammatory | Supporting brain metabolism | *Proteus mirabilis* | Grujic *et al.* (2015) |
| 54 | *Vitex negundo* | *Essential oils* | *Tocopherol, β-carotene and lycopene* | Leaves | Anti-microbial, anti-inflammatory, antipyretic | Wound, ulcer, asthma | *Escherichia coli* | Namsivayam and Roy (2013) |
| 55 | *Zingiber officinale* | *Phenolic* | *Sinapic acid* | Root | Antitumorigenic and anti-inflammatory | Arthritis, rheumatism, muscular aches, pains, sore throats, dementia | *Pseudomonas aeruginosa* | Silva and Domingues (2015), Ali *et al.* (2008), Rahmani *et al.* (2014) |

(Park *et al.* 2008). Alkaloids have the ability of disrupting fimbriae and other adhesions that enhance cell adhesion and biofilm formation.

Bioactive compounds like terpenoids, linalool (3,7-dimethylocta-1,6-dien-3-ol) and phenyl propanoids (eugenol, 4-allyl-2-methoxyphenol) are the major components of clove (*Syzygium aromaticum*) oil (Khan *et al.* 2013). These compounds show excellent synergistic activities and decrease the minimum inhibitory concentration of various conventional antibiotics like gentamicin, vancomycin and beta-lactams. Combination of eugenol and other metabolites like cinnamate, cinnamaldehyde, thymol or carvacrol enhances the antimicrobial activity of the compounds (Molina *et al.* 2012). This synergistic effect depends on eugenol's ability to damage the membrane of Gram-negative bacteria the amount of lipoproteins and lipopolysaccharides present, which restricts the diffusion of hydrophobic compounds inside the biofilms.

## 1.5 *Mechanism of action*

1.5.1 *Alkaloids:* A vast category of plant secondary metabolites falls under alkaloids. Antimicrobial and anti-biofilm properties of alkaloids have been investigated in different sub-classes like quinolone, agelasine, indolizidine, isoquinoline etc. (figure 2). The mode of action of all these derivatives is also different and it depends on the bioactive nature of the compounds as well as the microorganisms on which these bioactive compounds act.

Many alkaloids like quinoline or quinolone-based compounds act against bacterial cells by destroying their cell-membrane integrity. For example, a quinoline-derived antimicrobial molecule HT61 is able to disrupt the bacterial membrane by depolarizing it and discharging the intercellular constituents at concentrations both above and below the minimum inhibitory concentration of the drug molecule (Hubbard *et al.* 2017). HT61 is a cationic molecule that is attracted toward negatively charged bilayers by virtue of electrostatic interactions, partitioning into the membrane and causing structural changes. Automatically, this helps in stimulating the interaction of the membrane with cationic substrates which finally causes depolarization of the cell membrane, leading to the leakage of cytoplasmic contents.

In a number of studies it has been observed that alkaloids of the isoquinoline class like berberine may act as a DNA ligand and are able to bind with both single- and double-stranded DNA, which subsequently may cause DNA damage (Hou *et al.* 2017). In general, the causative agents of DNA damage induce the SOS repair genes. But these alkaloids act without affecting both DNA replication and SOS response In recent studies, it has been proposed that compounds like berberine inhibit a major and highly conserved bacterial protein named Ftsz. Ftsz-GFPase helps in the formation of the z-ring, the earliest known step for the occurrence of cytokinesis in bacteria (Sun *et al.* 2014).

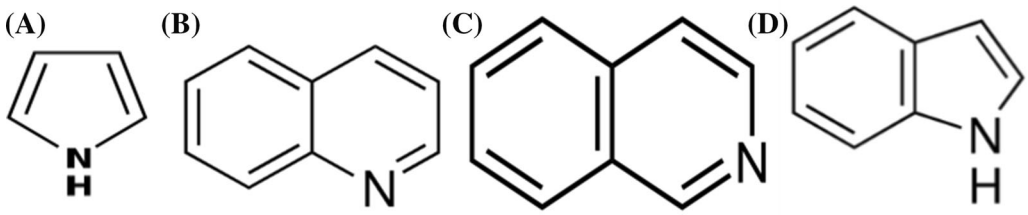


**Figure 2.** Basic structures of alkaloids: (**A**) pyrrole, (**B**) quinoline, (**C**) isoquinoline and (**D**) indole.

However, some researchers suggest that alkaloids like phenanthridine andisoquinoline act against biofilm bacteria by inhibiting nucleic acid synthesis and type-1 topoisomerases. The 3-carboxyl group present in the fluroquinolones helps in inhibition of Type-II topoisomerase enzyme (Aldred *et al.* 2014) on the other hand when the bacterial cells are treated with methyl quinolone acts as a respiratory inhibitor by restricting $O_2$ consumption.

1.5.2 *Essential oils:* Like alkaloids, essential oils also fall under the vast category of plant-derived compounds. Many of these compounds have a lot of similarities in their modes of action but a lot of dissimilarities can also be observed.

The most elucidated action of major essential oils depends upon their interaction with the cell wall and membrane. Compounds like carvacrol, thymol etc. can cause severe damage to the envelope of both Gram-positive and Gram-negative bacteria and inhibit growth (Nazzaro *et al.* 2013). When *E. coli* and *Salmonella enterica* etc. are exposed to allyl isothiocyanate, the main component of mustard essential oil, and observed under a scanning electron microscope, the imperfection of the cell membrane and unfinished cellular shape can be seen. Treatment of *E. coli* with Spanish oregano can create sizable holes on the cell wall, providing evidence for the previously stated mechanism of action of essential oils (Faleiro 2011). Eugenol, one of the major essential oils, when treated with *S. cereviseae, E. coli or B. subtilis* can cause similar type of deformity of the cell membrane. Sometimes, due to the disintegration of the cell membrane, intracellular potassium leakage takes place, also there is an imbalance in the membrane potential because of leakage of phosphate ions (Bennis *et al.* 2004). Thus, essential oils can not only be used as antimicrobial agents, but they can also be used to enhance the activity of traditional antibiotics (Omojate *et al.* 2014).

1.5.3 *Coumarins:* Coumarins such as xanthotol, esculetin (6,7-dihydroxycoumarin), and daphnetin (7,8-dihydroxycoumarin) are major plant derivatives produced by a wide range of plants. Recent studies have reported that these plant metabolites exhibit strong antimicrobial, antioxidant as well as antibiofilm activities on both Gram-positive and Gram-negative bacteria – especially on Gram-negative bacteria because of its strong bioactive nature. Though the proper mechanism of the antimicrobial activity of coumarins is still not clear, experiments have shown that they can damage the cellular membranes of bacteria.

It has been proved that coumarins possess multiple substitution sites. Various substitutions in these sites subsequently change the nature and activity of coumarins. For example, hydroxyl substitutions of coumarins enhance the antimicrobial action, especially the substitution at C-6, C-7 and C-8 sites. It has been proposed that the hydroxyl substitution, especially at C-7 and C-8 sites, is able to activate the aromatic ring electrically, thus increasing the hydrophobicity and lipophilicity. This act consequently helps in promoting the interaction of different combinations of hydroxycoumarins with the cellular membrane, which induces the generation of irregular hollows on the cell membrane invading pathogens and causing irreversible damage (Yang *et al.* 2016).

Sometimes various pathogens harm the host cells by inducing oxidation. This oxidation may lead to the formation of free radicals transferring through chain reaction and causing damage to the normal functioning of the cells. Coumarins have the potential to defend these microorganisms by acting as a strong antioxidant (Al-Majedy *et al.* 2016). The antioxidant activity depends upon the hydrogen atoms of the amine group present in coumarins. Resonance and inductive effect subsequently influence this amine group. When coumarins react with free radicals due to the stable conformation of the free radical intermediates, they show scavenging properties, resulting in the abstraction of a hydrogen atom. However, the presence of thiodiazoles, triazoles and lactone rings and even steric hindrance can facilitate the antioxidant character (Widjaja *et al.* 2008; Gocer and Gulcin 2011).

1.5.4 *Lectins and polypeptides:* Although polypeptides were first reported to be restricting microbial growth in early 1942, the later extensive research activities on its inhibitory effects showed the potential of polypeptides as antimicrobial and antibiofilm agents. Though the mechanism of action is not clear enough, it has been presumed that its antimicrobial activity depends upon the formation of ion channels in the membrane of microbes or on the competitive inhibition of microbial proteins regarding adhesion to host polypeptide receptors.

Lectins are basically larger compounds having mannose-specific molecules obtained from plants (Upadhyay *et al.* 2014). The antibacterial activities of lectins affect both Gram-positive and Gram-negative bacteria. The carbohydrate-binding sites

present on the surface of the bacteria membrane play an important role in the recognition and binding of lectins. After recognition, lectins form complexes with the glycol conjugates present on the membrane. The intensity of antimicrobial activity depends on the linking of the carbohydrate structure – whether it is covalently linked, just like the linking between teichoic acid and polysaccharides (Cavalcante *et al.* 2014). Ultimately, this will cause severe disruption of the cell membrane, inhibiting the growth of the bacteria.

1.5.5 *Flavonoids, terpenoids, tannins, and phenolic compounds:* Bacteria have developed several fine-tuned systems to adequately and efficiently respond to environmental signals. The basic collective signaling process in biofilms is referred to as QS, which is a process by which bacteria produce and detect signal molecules that coordinate with their collective compounds in cell-density-dependent molecules. According to several lines of evidence, QS seems to play an essential role in the conversion of microcolonies into biofilm, and thus QS inhibitors can potentially halt the transition into the most recalcitrant stage (Nijveldt *et al.* 2001).

1.5.6 *Flavonoids:* Plant polyphenols are one large class of biologically active secondary metabolites of plants. Some of the major parts include secondary metabolites such as flavonoids, tannins, anthocyanins, phenolic acids, stilbenes, coumarins and lignans (Scalbert 1991). These substances play an important role in resistance against various microbial pathogens and protect against free radicals and toxins. Nowadays, plant polyphenols enjoy an ever-increasing recognition not only from the scientific community but also the general public because of their presence in fruits, seeds, vegetables and derived foodstuffs and beverages, whose regular consumption is beneficial to human health. They have often been highlighted due to their capacity for oxidative generation of free radicals that are effective in reducing the risk of some age-related degenerative diseases. In phenolic compounds, multiple mechanisms of antibacterial activity have been described (Slobodníková *et al.* 2016).

Majority of the identified QS inhibitor leads as well as the quorum quencher compounds are flavones (Nijveldt *et al.* 2001; Rafehi *et al.* 2012; Skogman *et al.* 2016). The mode of action of flavonoids includes interaction of phytochemicals with bacterial proteins and cell wall structures. They may cause damage to cytoplasmic membranes by reducing the fluidity of the membrane. However, some flavonoids show inhibition of nucleic acid synthesis, cell wall synthesis or energy metabolism.

1.5.7 *Terpenoids:* The antioxidant and antimicrobial activities of terpenoids basically depend on the components like terpinene-4-ol, 1,8-cineole, camphor, borneol, *p*-cymene, α-pinene and β-pinene. The main components of terpene oil, which account for 60.7% of the total, are eucalyptol, camphor, β-pinene, borneol, terpinen-4-ol and α-pinene and they individually act as antioxidative agents in different antimicrobial-inhibiting mechanisms. α-Terpineol (a monoterpene alcohol) and linalool (an acyclic terpene alcohol) show that they are more active antimicrobial agents than eucalyptol which is having almost no antioxidant activity. Sesquiterpene hydrocarbons and the oxygenated derivatives of terpenoids have very low antioxidant activity as well as the ability to inhibit nucleic acid synthesis. The mechanism of action can also be attributed to the anti-cell-adhesion properties of terpenoids and the calcium stress generated along the membrane.

1.5.8 *Tannins:* Plants produce many compounds that are biologically active, either as part of their normal program of growth and development or in response to pathogen attack. Bioactive compounds of tannins from extracts of *A. colubrina*, *C. leptophloeos* and *M. urundeuva* affect different communities of microorganisms that are very much responsible for causing infectious diseases, such as cough, bronchitis, influenza, urinary/liver diseases, ulcerative external lesions and ovarian inflammation (Hierholtzer *et al.* 2013).

PACs are highly complex structures (mostly composed of profisetinidin in *A. colubrina* and prorobinetinidin in *C. leptophloeos*) that inhibit the adhesive nature of biofilms. Similarly, hydrolyzable tannins (consisting of gallic acid units in *M. urundeuva*) can induce damage in *P. aeruginosa*, providing bacteriostatic and anti-adhesive effects (Mierziak *et al.* 2014).

The anti-biofilm mechanism of tannins can also be supported by the interaction of bioactive compounds or phytochemicals with cell adhesion receptors. Sometimes these interactions lead to the formation of ion channels in the membrane which cause imbalance of the electric potential.

Table 2 lists the major bioactive compounds extracted from plants and table 3 shows a comparative mechanism of action of various phytochemicals and antibiotics.

## 1.6 *Qualitative phytochemical screening*

To determine the chemical composition of the extracts and to find out the presence of bioactive compounds, certain phytochemical reactions need to be performed. Hence, plant extracts of 3–5 mg/mL concentration were suspended in 1 mL of absolute alcohol or distilled water.

1.6.1 *Detection of triterpenes/steroids:* A volume of 1 mL of acetic anhydride and few drops of sulfuric acid ($H_2SO_4$) are added to the ethanolic solution of plant extracts. Violet to blue color change indicates the presence of steroids, whereas formation of blue-green rings represents the existence of terpenoids. The test is known as Liebermann–Burchard test (Fawehinmi *et al.* 2013).

**Table 3.** Comparative analysis of mechanism of action of phytochemicals and antibiotics

| Sl. no. | Bioactive compound | Phytochemicals | Mechanism of action | Similar action through antibiotics | References |
|---|---|---|---|---|---|
| 1 | Flavonoid | *Amentoflavone* | Induction of fungal apoptosis | Neomycin/polymyxin sulfamethoxazole-trimethoprim (Bactrim, Bactrim DS, Septra) | Hwang *et al.* (2012) |
| | | *Isoquercitrin* | Disruption of cell membrane | Dalbavancin (Dalvance) | Lee and Lee (2015) |
| | | *Catechin* | Damage in cell wall | Dalbavancin (Dalvance) | Lee and Lee (2015) |
| 2 | Terpenoid | *Carvacrol* | Inhibition of cell adhesion, calcium stress | Bacitracin/neomycin/polymyxin B) | Lee and Lee (2015) |
| | | *Eugenol* | Disintegration of cell membrane, ergosterol biosynthesis inhibition, influences cytoplasmic permeases | Telavancin (Vibativ) vancomycin (Vancocin) | Lee and Lee (2015) |
| | | *Caffeic acids* | Biofilm inhibition | Bacitracin/neomycin/polymyxin B) | Lee and Lee (2015) |
| | | *Quercetin* | Inhibition of cell adhesion | Telavancin (Vibativ) | Lee and Lee (2015) |
| | | *Galangin* | Biosynthesis inhibition | Telavancin (Vibativ) | Lee and Lee (2015) |
| | | *Apigenin* | Damage in cell wall | Telavancin (Vibativ) | Lee and Lee (2015) |
| | | *Kaemopferol* | Induction of fungal apoptosis | Lymyxin B | Lee and Lee (2015) |
| | | *O-coumaric acid* | Induction of fungal apoptosis | Lymyxin B | Lee and Lee (2015) |
| 3 | Alkaloid | *Squalamine* | Disintegration of cell membrane due to electrostatic interaction with the cell surface receptors | Imipenem/cilastain (Primaxin) | Salmi *et al.* (2008) |
| | | *Isoquinoline* | Inhibition of nucleic acid synthesis | Meropenem (Merrem) | Tominaga *et al.* (2002) |
| | | *Berberine* | Act as DNA ligand causing DNA damage | Doripenem (Doribax) | Boberek *et al.* (2010) |
| 4 | Carotenoid | *Lycopene* | Deformation of membrane, induction of fungal apoptosis | Sulfamethoxazole-trimethoprim (Bactrim, Bactrim DS, Septra) | Lee and Lee (2015) |
| 5 | Saponin | *α-Tomatine* | Induction of fungal apoptosis, disruption of cell membrane | | Hwang *et al.* (2012) |
| 6 | Polyphenol | *Curcumin* | Formation of pore on membrane, ROS, inhibition of morphogenetic switch | Clindamycin (Cleocin) | Lee and Lee (2014), Sharma *et al.* (2010) |
| | | *Resveratrol* | Induction of fungal apoptosis | Lincomycin (Lincocin) | Lee and Lee (2015) |
| 7 | Lectins and polypeptides | | Interaction with cell adhesion receptors, formation of ion channels in the membrane | Amoxicillin/clavulanate (Augmentin) | Upadhyay and Upadhyaya (2014) |
| 8 | Coumarins | *Hydroxycoumarins* | Cell membrane damage, antioxidation | Doxycycline | Al-Majedy *et al.* (2016) |
| | | *Xanthotol, esculetin, daphnetin* | Free-radical formation | Tetracycline | Al-Majedy *et al.* (2016), Widjaja *et al.* (2008) |
| 9 | Essential oils | *Eugenol* | Membrane potential disbalance, disintegration of cell membrane | Polymyxin B | Zhang *et al.* (2017) |
| | | *Thymol* | Pore formation on cell wall | Polysporin, clindamycin (Cleocin) | Faleiro (2011) |
| 10 | Tannin | *Cyanidin* | Prevent biofilm formation on the polystyrene surface | Telithromycin | Al-Majedy *et al.* (2016) |
| | | *Catechin* | Interaction with cell adhesion receptors, formation of ion channels in the membrane | Telithromycin | Al-Majedy *et al.* (2016) |
| | | *Epicachin* | Pore formation on cell wall | Temafloxacin | Al-Majedy *et al.* 2016) |
| 11 | Other phenolic compounds | *Rosmarinic acid* | Disintegration of cell membrane | Trovofloxacin | Hwang *et al.* (2012 |
| | | *Isoflavonoids* | Cell membrane damage, antioxidation | Trovofloxacin | Hwang *et al.* (2012) |

1.6.2 *Detection of coumarin:* Few drops of alcoholic sodium hydroxide (NaOH) were added to 2–3 mL of sample solution. Appearance of yellow color represents the presence of coumarin. For confirmation, 1 mL of 5N HCl is added to the solution; the test is considered positive if it turns into a colorless solution (Jacob and Shenbagaraman 2011).

1.6.3 *Detection of alkaloid:* 1% aqueous solution of HCl is added to the sample and filtered into two test tubes. If an orange–red precipitate is formed after the addition of Dragendorff's reagent, the test is said to be positive. To the second test tube, 1 mL of Mayer's reagent is added. In this case, the formation of buff-colored precipitate is an indication of the presence of alkaloids (Wagner and Bladt 2001).

1.6.4 *Detection of sesquiterpene lactones:* Screening for sesquiterpene lactones is done by Baljet test. At first, 1% picric acid is prepared by mixing 1 g of picric acid with 100 mL of ethanol; at the same time, 10% NaOH solution is prepared. Both of them are mixed together at a ratio of 1:1 and 1 mL of sample extract is added to it. If the solution is transformed into an orange-red color, the test is considered to be positive (Sánchez *et al.* 2016).

1.6.5 *Detection of quinone:* The plant extract solution is treated with few drops of concentrated sulfuric acid. The presence of quinone is confirmed by the formation of red color in the sample (Dominguez 1973).

1.6.6 *Detection of carboxyl group:* 10 drops of 10% sodium bicarbonate solution is added to the sample. Due to the production of carbon dioxide, if the bubble formation is visible, the test is considered positive (Dominguez 1973).

1.6.7 *Detection of tannins:* About 0.5 g of powdered sample is mixed with 10 mL of distilled water. Few drops of 1% ferric chloride is added to the filtered solution. The appearance of bluish black or greenish black coloration is an indication of the presence of tannins (Firdouse and Alam 2011).

1.6.8 *Detection of saponin:* 0.5 g of sample solution is dissolved in 10 mL of deionized water in a test tube and shaken vigorously. The test tube is then positioned vertically. If a copious foam layer is formed above the surface of the liquid, the sample is considered to contain saponin (Rathore *et al.* 2012).

## 2. Conclusion

Biofilm-associated bacterial infections frequently caused by *S. epidermidis, S. aureus*, *E. coli*, and *P. aeruginosa* are found in majority of human diseases. The effectiveness of many antimicrobial drugs has been lost due to the evolution of pathogenic resistance. Thus, microorganisms are no longer susceptible to most of the existing antibiotics and therapeutic agents (Römling and Balsalobre 2012). Various groups of plants having different medicinal properties have a potential to cure these diseases. In this review we have described that various parts of plants have the ability to inhibit biofilm formation of different bacterial strains that were isolated from different sources of infection such as wounds, uro-catheter infections and septicemia. The development of resistance to antibiotics has resulted in the development of biofilms by microbial pathogens. Therefore, alternative ways of reducing biofilms are very essential. The anti-adherence and anti-QS compounds present in plants (extracts from leaves, barks, flowers, and roots) help in enhancing the susceptibility of the bacteria and thus in eradicating biofilms. Thus, this hints that the plant extracts are going to play a major role in the quest of the future generation for medicines to deal with the problems of biofilm formation and to find a herbal solution to antimicrobial resistance.

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