Biofilms comprise multiple microorganisms that are found to be and Singh for the failure of clinical therapy associated with biofilms (Parsek and 2003). Biofilm offers cell-to-cell communication and helps in protecting the micro-organisms to survive in unfavorable conditions (Parsek and Surette, 2006; West et al., 2012). EPS helps in protecting the microorganism from immune response and antimicrobial agents. It helps microorganisms to survive in unfavorable conditions (Parsek and Singh, 2003). Biofilm offers cell-to-cell communication and horizontal gene transfer (Keller and Surette, 2006, West et al., 2006), hence they develop antibiotic resistance. These are the main reason for the failure of clinical therapy associated with biofilms (Parsek and Singh, 2003; Donlan and Costerton, 2002; Hall et al., 2004). Biofilms comprise multiple microorganisms that are found to be associated with the biotic and abiotic surfaces. Biofilms can be either single or multilayered and can have either homogenous or heterogeneous populations of bacteria which remain in the matrix, made up of extracellular polymeric substances, secreted by constituent population of the biofilm (Gupta et al., 2016). Different biofilms differ from their free-living counterparts in their growth rate, constitution, structure and increased resistance to biocides, antibiotics and antibodies by virtue of up-regulation and/or down regulation of approximately 40% of their genes. This makes them highly difficult to eradicate with therapeutic doses of antimicrobial agents (Prakash et al., 2003).

Most of the biofilm cells and planktonic cells normally killed by drug treatment. However, drug tolerant persists disseminate into single microbial cell and start a new cycle of biofilm development (Lewis, 2010; Keren et al., 2011; Zhang, 2014) which subsequently increases the duration of treatment of diseases, caused by biofilm forming pathogenic microorganisms. The structure and physiological characteristics of the formed biofilms are mainly responsible for antimicrobial resistance (Garg and Azmi, 2017). The bacteria residing within biofilms are generally antibiotic tolerant and susceptible to antibiotics or other chemicals upon dispersal from biofilm. This suggests that microbial capacity of survival against antibiotics is due to phenotypic adaptability and not essentially due to genetic adaptability (Anwar et al., 1989). Factors such as mechanical stress,
enzymatic digestion, pH, oxygen availability, temperature and limiting nutrition trigger dispersal of cells from the biofilm. Biofilms induced due to low oxygen condition whereas normoxia decreases biofilm formation (Totani et al., 2017). Further, enhanced bacterial respiration reduces the persisters in bacterial population (Vilcheze et al., 2017). Quorum sensing (QS) is the mode of cell-to-cell communication in biofilms. QS is operated by autoinducing peptides (AIPs) in Gram-positive bacteria and N-acyl-homoserine lactones (lipids molecules) in Gram-negative bacteria. Biofilms can develop on both animate and non-animate substances. The 65-80% of human clinical infections are associated with biofilm formation (Pletzer and Honcock, 2016). Biofilms can be formed on all types of materials including medical implants living cells and instruments (Donelli and Francolini, 2001). Public health is facing a biggest threat due to the development of antibiotic resistant varieties of pathogens (Byarugaba, 2004; Okeke et al., 2005). These bacteria can even survive the treatments of UV lights, heavy metal, acidity, changes in hydration or salinity (Espeland and Wetzel, 2001; Le et al., 2000; Leid et al., 2002; McNeill and Hamilton, 2003; Teitzel and Parsek, 2003). Biofilm degradation by antibiotics requires high MIC and MBC value, which can be fatal when used in vitro (Wu et al., 2015; Hengzhuang et al., 2011; Hoiby et al., 2011).

Further, the ability of pathogens to cause infection is depend on the secretion of agents, termed as virulence factors, such as toxins and adhesion molecules, that actively cause damage to host tissues. The increasing attention has been given in recent years to ‘disarm’ the pathogenicity of bacteria rather than killing them. This can be done by targeting virulence using anti-infective or anti-virulence drugs. Search for more antimicrobial compounds is continuously going on due to limitations of present therapy regimens and phytochemicals are now considered as an important source of antimicrobial agents for biofilm degradation (Rasooli et al., 2008; Koo et al., 2010; Shaye gh et al., 2008). Majority of the phytochemicals can act synergistically with antibiotics and some of them are very effective alone too. Phytochemicals have a broad spectrum of action including bacteria, insects, nematodes, fungi and yeast (Abreu et al., 2013). Phytochemicals work by damaging the microbial membrane structure, inhibiting peptidoglycan synthesis, modifying bacterial surface hydrophobicity and modulating quorum-sensing (QS) (Rasooli et al., 2008). Phytochemicals have reported to be used as QS inhibitors and help to overcome the selective pressure created by antibiotic use (Borges et al., 2014).

2. Types of biofilm
Biofilms can be formed on both animate and inanimate things. Biofilms can easily develop on the inert surfaces of medical devices, contact lenses and catheters or living tissues, as on epithelium of the lungs (particularly in cystic fibrosis patients), on the endocardium and wounds (Aleksandra et al., 2012). Biofilm can also found to be associated with diseases like endocarditis, periodontitis, rhinosinusitis and osteomyelitis (Figure 1), but more commonly seen in medical implants and urinary catheters. These infections can often only be treated by removal of the implant which increase the trauma to the patient and the cost of treatment.

**Biofilm in Human Health and Diseases**

- **Tonsillitis and pharyngitis**
- **Sinusitis**
- **External otitis**
- **Bronchiolitis**
- **Diphtheria**
- **Otitis media**

**Infectious diseases of ear, nose, and throat**

- **GI tract infections**
- **Urinary tract infections**
- **Skin infections**

**Other biofilm mediated diseases**

- **Tuberculosis**
- **Whooping cough**
- **Myocarditis, pericarditis** (meningococcal meningitis)
- **Endocarditis**
- **Pneumonia**
- **Cystic fibrosis**

**Infectious diseases of the heart and lungs**

- **Conjunctivitis**
- **Dacryocystitis** (infection of lacrimal sac)
- **Bacterial corneal ulcer**

**Dental health**

- **Dental caries**
- **Periodontal disease**
- **Halitosis**
- **Dental unit waterlines**

**Infectious diseases of the eye**

- **Heart and lungs**

**Figure 1:** Association of biofilm with various diseases.
2.1 Biofilms on medical devices

A list of medical devices having biofilms colonization was provided by Costerton et al. (1999).

2.1.1 Prosthetic heart valves (PHV)

The surgical implantation of prosthetic valve damages the tissue which results in the accumulation of platelets and fibrin at the suture site and on the device.

Sewing cuff fabric of PHV gets colonized by microorganism (Illingworth et al., 1998). Coagulase negative Staphylococcus is the main inhabitants in early stage of prosthetic valve endocarditis (PVE) due to initial contamination of the surroundings (Hancock et al., 1994; Karchmer and Gibbons, 1994). In the later stage of PVE (after 12 months of valve replacement), infection is mainly caused by Streptococci, Coagulase negative Staphylococcus, Enterococci, Staphylococcus aureus, Gram-negative Coccobacilli, or fungi (Karchmer and Gibbons, 1994). However, despite major advances in cardiovascular surgical protocols and use of antimicrobial drugs, PVE continues to complicate the course of 1.4 and 3.1% of patients after cardiac valve replacement within 12 months of valve replacement (Douglas and Cobb, 1992).

2.1.2 Central venous catheters (CVC)

Catheters are medical devices that can be inserted in the body to treat disease or perform a surgical procedure. Among indwelling medical device, CVCs accounts for the maximum device related infection ranging from 3.5% (Maki, 1994). The device becomes coated with platelets, plasma and tissue proteins such as albumin, fibrinogen, fibronectin and laminin as it comes in direct contact with the bloodstream (Raad, 1998). The S. aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis and Candida albicans are the main CVC infection causing organisms (Elliott et al., 1997; Raad, 1998).

2.1.3 Contact lenses

Bacteria adhere rapidly to both soft and hard types of contact lenses (Miller and Ahearn, 1987; Stapleton et al., 1993; Stapleton and Dart, 1995). P. aeruginosa, S. aureus, S. epidermidis, Serratia spp., E. coli, Proteus spp. and Candida spp and protozoan Acanthamoeba are the main inhabitants (Dart, 1996; McLaughlin et al., 1998). The development of biofilms has even been observed on the storage cases of the lenses (Dart, 1996; McLaughlin et al., 1998; Wilson et al., 1991).

2.1.4 Intra uterine devices (IUD)

The IUDs play an important role in cause and spread of pelvic inflammatory disease (Wolf and Kreger, 1986; Chesney, 1994; Lewis, 1998). The species of Corynebacterium, Micrococcus and Enterococcus along with Lactobacillus plantarum, group B streptococci, Streptococcus epidermidis, Candida albicans and S. aureus have been isolated from IUDs (Marrie and Costerton, 1983). The heavy contamination of IUDs with S. epidermidis, enterococci and anaerobic lactobacilli has also been reported (Wolf and Kreger, 1986).

2.1.5 Urinary catheters

The urinary catheters are silicon and latex tubular devices which are used in treatment of urinary system related problems (Kaye and Hessen, 1994). The 10-50% of catheterization for short periods of time (6-7 d) causes infection whereas almost all long term catheterization (>28 d) leads to bacteriuria (Stickler, 1996). Microorganism enters into the urethra or bladder directly with the insertion of the catheter, through its tubes and collecting bags or through the exudates sheath that surrounds the catheters (Kaye and Hessen, 1994). The S. epidermidis, Enterococcus faecalis, E. coli, Proteus mirabilis, Providencia stuartii, P. aeruginosa and Klebsiella pneumoniae are the initial inhabitants of these devices (Stickler, 1996). Other organisms like Morganella morganii, Acinetobacter calcoaceticus and Enterobacter aerogenes were also detected in the biofilm (Stickler et al., 1993).

2.2 Biofilm on various organs

Biofilm can also very frequently reside in various organs and cause infections.

2.2.1 Middle ear

Otitis media is a common children disease which occurs due to the inflammation of the mucoperiosteal lining of middle ear. Typanostomy tubes are used in such conditions to prevent the pressure and hearing loss. These tubes can develop biofilm on their inner surfaces (Biedlingmaier et al., 1998). P. aeruginosa, S. aureus, S. epidermidis and S. aureus biofilms were observed in armstrong-style silicone tubes (Biedlingmaier et al., 1998; Saidi et al., 1999). Along with antibiotic resistance of biofilm, middle ear fluid is less penetrated by antibiotics due to the formation of biofilm (Krause et al., 1982).

2.2.2 Prostate gland

Bacteria from urethra and infected urine can ascend into the prostate gland and cause chronic bacterial prostatitis. The E. coli was found to be most common isolate, however, Klebsiella, enterobacteria, Proteus, Serratia, P. aeruginosa, Staphylococcus, coryneforms, and E. faecalis were also isolated from an infected prostate gland. In another study conducted by Nickel and Costerton (1993), E. coli, P. aeruginosa, Bacteroides spp., Gardnerella spp., Corynebacterium spp. and coagulase negative Staphylococcus were observed to inhabit the prostate gland. Bacteria get a hostile environment in prostate gland, develop glycocalyx covering around them and become inactive. This inactivation makes it more difficult for antibiotics to kill these bacteria and that's why prostate gland infection is generally difficult to treat (Domingue and Hellstrom, 1998).

2.2.3 Teeth

Moore et al. (1983) observed several types of bacteria which are present on the teeth of the patient of a periodontal disease. These were Fusobacterium nucleatum, Peptostreptococcus micros, Eubacterium timidum, Eubacterium brachy, Lactobacillus spp., Actinomyces naeslundii, Pseudomonas anaerobius, Eubacterium spp strain D8, Bacteroides xintermedius, Fusobacterium spp, Selenomonas sputigena, Eubacterium spp strain D6, Bacteroides spermomisentes and Haemophilus aphrophilus (Moore et al., 1983). A protein layer called pellicle develops around the teeth right after
it was cleaned and with layers of Gram-positive cocci and rod shaped bacteria mainly streptococci, actinomycetes, and smaller numbers of *Haemophilus* (Marsh, 1995). These cells develop the extra polymeric matrix around them after few days and now onwards actinomycetes were found to be in dominant numbers (Marsh, 1995). A layer of plaque is formed 2-3 weeks later and mineralized plaque with calcium and phosphate is called calculus or tartar (Shapiro and Stallard, 1997; Lamont and Jenkinson, 1998).

### 2.2.4 Heart valve

Bacteria and fungi can infect various heart valves and cause valve endocarditis (Livornese and Karzeniowski, 1992). *Streptococci, Enterococci, Pneumococci, Streptococcus bovis,* Staphylococci, Gram-negative bacteria and fungi (*Candida* and *Aspergillus spp.*) were found as the infecting microorganism (Tunkel and Mandell, 1992).

### 2.2.5 Cystic fibrosis (CF)

It is a genetically transferred respiratory disorder in which a viscous mucus secretion covers the respiratory epithelium (Koch and Hoiby, 1993). This mucus increases the chances of bacterial and fungal lung infections (May et al., 1991). The lungs of nearly all CF patients are chronically colonized by *P. aeruginosa,* which significantly reduces life expectancy of individual. It is the leading cause of morbidity and mortality for CF patients. At the initial stage of infection, the microorganisms are non-mucoid type but with their prolonged and demanding stay in the lungs, they become mucoid. The biofilm formed by *P. aeruginosa* protects them from immune system defense actions and effect of antibiotics (Koch and Hoiby, 1993). This mucoid secretion is of a polysaccharide material called as alginate (Lam et al., 1980). Microorganisms can adopt other defense methods to get protected. One of such ways has been studied by Cochrane et al. (1988). They found that bacteria can produce an iron rich protein in order to survive in the low level of iron in blood of the host. The *S. aureus* and *Haemophilus influenzae* makes lungs susceptible to colonization of *P. aeruginosa* (Govan and Deretic, 1996). Pyocyanin produced by *P. aeruginosa* act as both a virulence factor and a quorum sensing signaling molecule for *P. aeruginosa* (Lau et al., 2004; Karatuna and Yagci, 2010). It has been identified that pathogen-associated proteins have homology only with pathogenic bacteria and not with non-pathogens (Ho Sui et al., 2009). Such types of proteins are more likely to have virulence-related functions. The identified pathogen-associated proteins have been included in components of the phenazine biosynthesis pathway and, hence pyocyanin biosynthesis is an attractive target for anti-infective drug intervention. The time period of infection affects its chances to getting cured and it has been reported that early infection can be controlled easily as compared to an old one (Anwar et al., 2017).

Prior to the commercial use of phytochemicals, various antibiotics and others chemicals have been involved in removal of biofilms. In *P. aeruginosa,* clarithromycin blocks biofilm matrix formation (Yasuda et al., 1993). The overall thickness of the biofilm reduces by ciprofloxacin and exposes the immature biofilm to phagocytosis by polymorphonuclear neutrophils and the matrix polymer of biofilm in *S. aureus* was dissolved by streptokinase (Nemoto et al., 2000). The acyl-homoserine lactone interferes with cellular signalling mechanisms which have been used for QS adversely affects normal biofilm formation (Parsek and Greenberg, 2000). However, due to the antibiotic resistance of biofilm-associated bacteria, alternate and efficient tools are needed to overcome these limitations and the use of different enzyme is one of the most promising approaches.

The composition of the EPS matrix has been studied in bacteria such as *P. aeruginosa,* *Bacillus spp., staphylococcus spp.* and *streptococcus spp.* The constituent of extracellular matrix depends on the environment and the type of bacteria present within the biofilms. The main component of biofilms is DNA, polysaccharides, proteins, and EPSs and the degradation of matrix components can weaken or disperse biofilms. The use of various reagents can leads to complete an effective disruption of the biofilms architecture (Fleming et al., 2017). The EPS matrix also acts as a diffusion barrier to delay the infiltration of some antimicrobial agents (Xu et al., 2000). The reactive chlorine species in a number of these agents deactivated at the surface layers of the biofilm before they are not able to disseminate into the interior of the biofilm (de-Beer et al., 1994). A study showed that oxacillin, cefotaxime, and vancomycin had reduced the penetration throughout *S. aureus* and *S. epidermidis* biofilms (Singh et al., 2010). However, with the emergence of multidrug resistant of *S. aureus,* the need for more effective treatments of biofilm-associated infections becomes imperative (Kalia and Purohit, 2011; Pooi and Yien, 2014). The biofilm matrix is composed of a variety of diverse components and its resistance to antibiotics indicates that the disruption of the biofilm structure could be achieved via the degradation of individual biofilm compounds by various therapeutic molecules (Aleksandra et al., 2012) and this phenomenon creates an opportunity for use of different phytochemicals as alternate for the disruption of biofilm integrity. The target areas for different reagents for control and management of biofilms have been summarized in Figure 2.

![Target areas of different reagents for control of biofilms](image)

**Figure 2:** Target areas of different reagents for control of biofilms.

3. **Target areas of phytochemicals**

The phytochemicals represent the richest available reservoir of novel therapeutics (Manoharachary and Nagaraju, 2016; Nooreen et al., 2018; Dang, 2018) (Table 1). The antimicrobial activities of plant extracts are beyond doubt, in many instances; however, their exact mechanism of antimicrobial functionality is not well understood. Volatile oils plant origin are frequently used as antibacterial agents because of their feasibility and safety (Fahim et al., 2017).
### Table 1: Various groups of phytochemicals and their antimicrobial activity

| Phytochemicals       | Plant source                          | Microorganisms                                                                 | References                                             |
|----------------------|---------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------|
| **Phenylpropanoids** |                                       |                                                                               |                                                        |
| **General mechanism of action:** Inhibition of energy generation by inhibiting glucose uptake or utilization of glucose and affects on membrane permeability. |                                                        |                                                        |
| Eugenol              | Various species                       | P. aeruginosa PAO1                                                             | Zhou et al., 2013                                      |
|                      |                                       | K. pneumoniae                                                                 | Matsesh et al., 2013                                   |
|                      |                                       | L. monocytogenes                                                              | Upadhyay et al., 2013                                  |
| Cinnamaldehyde       | Cinnamomum sp.                        | L. monocytogenes                                                              | Upadhyay et al., 2013                                  |
|                      |                                       | Vibrio spp.                                                                   | Brackman et al., 2008                                 |
|                      |                                       | S. epidermidis                                                                | Sharma et al., 2014                                   |
|                      |                                       | C. sakazakii                                                                  | Amalaradjou and Venkitanarayanan, 2011                |
| **Benzolic acid derivatives** |                                       |                                                                               |                                                        |
| **General mechanism of action:** Enzyme inhibition and non specific interaction with proteins. |                                                        |                                                        |
| Vanillin             | Vanilla planifolia Jacks              | C. violaceum CV026, A. hydrophila                                             | Ponnusamy et al., 2009                                 |
|                      |                                       | P. aeruginosa PAO1                                                             | Kappachery et al., 2010                               |
|                      |                                       | A. tumefaciens CS8                                                            | Plyuta et al., 2013                                   |
| Gallic acid          | Various species                       | P. aeruginosa PAO1                                                             | Plyuta et al., 2013                                   |
|                      |                                       | A. tumefaciens CS8                                                            | Plyuta et al., 2013                                   |
|                      |                                       | S. epidermidis                                                                | Moran et al., 2014                                   |
|                      |                                       | E. corrodens                                                                  | Matsunaga et al., 2010                                |
|                      |                                       | C. violaceum ATCC 12472                                                      | Borges et al., 2014                                   |
| Ellagic acid         | Various species                       | B. cepacia, P. putida pKR–C1                                                  | Huber et al., 2003                                    |
|                      |                                       | C. violaceum, S. dysgalactiae                                                 | Huber et al., 2003                                    |
|                      |                                       | S. aureus ATCC 11632                                                          | Ta et al., 2014                                       |
|                      |                                       | C. albicans ATCC 90028                                                        | Durig et al., 2010                                    |
|                      |                                       | E. coli ATCC 10536                                                            | Bakkiyaraj et al., 2013                               |
| **Tannins**          |                                       |                                                                               |                                                        |
| **General mechanism of action:** Binds to proteins, enzyme inhibition and substrate deprivation. |                                                        |                                                        |
| Punicalagin          | Punica granatum and Combretaceae species | C. violaceum, S. typhimurium SL 1344                                          | Li et al., 2014                                       |
| Tannic acid          | Various species                       | P. aeruginosa PA14, P. putida pKR–C12, E. coli MT102                           | Huber et al., 2003                                    |
|                      |                                       | S. aureus                                                                    | Cho et al., 2013                                      |
| **Stilbenes**        |                                       |                                                                               |                                                        |
| **General mechanism of action:** DNA damage, cell division impairment, oxidative membrane damage, and metabolic enzymes inhibition. |                                                        |                                                        |
| Resveratrol          | Vitaceae and Ericaceae species         | S. epidermidis, S. aureus                                                     | Moran et al., 2014                                   |
|                      |                                       | P. aeruginosa PA14, E. coli O157:H7                                           | Cho et al., 2013                                      |
|                      |                                       | P. acnes                                                                      | Coenev et al., 2012                                   |
| Pterostilbene        | Various species                       | C. albicans SC5314, C. albicans Y0109, C. albicans 0304103, C. albicans 01010 | Li et al., 2014                                      |
### Flavonoids
**General mechanism of action:** Binds to adhesions, complex with cell wall, inactivate enzymes.

| Flavonoid | Source | Organism | Source | Reference |
|-----------|--------|----------|--------|-----------|
| Quercetin | Various species | *E. coli* O157:H7, *V. harveyi* BB120 | | Vikram et al., 2011 |
| Epicatechin | *Camellia sinensis* | *E. coli* JDL271/Pa1105, *P. aeruginosa* PA01, *C. violaceum* ATCC 12472 | | Plyuta et al., 2013 |
| Gallo catechin | *Camellia sinensis* | *E. corrodens* | | Matsunaga et al., 2010 |
| Epigallocatechin | *Camellia sinensis* | *E. corrodens* | | Matsunaga et al., 2010 |

### Diaryleptanoids
**General mechanism of action:** Membrane permeabilization and membrane leakage in Gram-negative and Gram-positive bacteria.

| Diaryleptanoids | Source | Organism | Source | Reference |
|-----------------|--------|----------|--------|-----------|
| Curcumin | *Curcuma longa* | *S. epidermidis*, *P. aeruginosa* | | Sharma et al., 2014 |
| | | *S. mutans* UA159, *V. harveyi* | | Rudrappa and Bias, 2008 |
| | | *V. paraaeromlyticus*, *V. vulnificus* | | Hu and Chen, 2013 |
| | | *E. coli*, *P. aeruginosa* | | Packiavathy et al., 2013 |
| | | *P. mirabilis* | | Packiavathy et al., 2014 |
| | | *C. albicans* | | Shahzad et al., 2014 |

### Monoterpenes
**General mechanism of action:** Change in the transmembrane potential and membrane perforation.

| Monoterpenes | Source | Organism | Source | Reference |
|--------------|--------|----------|--------|-----------|
| Thymol | *Thymus vulgaris* | *L. monocytogenes* |
| | | *P. aeruginosa* ATCC 27853, |
| | | *P. aeruginosa* CIP A22 |
| | | *S. aureus* | | Upadhyay et al., 2013 |
| | | | | Soumya et al., 2011 |
| | | | | Qiu et al., 2010 |
| Carvacrol | *Thymus vulgaris* | *L. monocytogenes* |
| | | *P. aeruginosa* ATCC27853, |
| | | *P. aeruginosa* CIPA22, *P. aeruginosa* IL5 | | Upadhyay et al., 2013 |
| | | | | Soumya et al., 2011 |

### Sesquiterpenes
**General mechanism of action:** Strong inhibitors of biofilm formation and attachment.

| Sesquiterpenes | Source | Organism | Source | Reference |
|---------------|--------|----------|--------|-----------|
| Salvipisone | *Salvia sclarea* | *S. epidermidis* RP12 |
| | | *S. aureus* 1474 | | Kuzma et al., 2007 |
| | | | | Walencka et al., 2007 |
| Acanthospermolide | *Acanthospermum hispidum* | *P. aeruginosa* | | Cartagena et al., 2007 |

### Triterpenoids
**General mechanism of action:** Strong inhibitors of biofilm formation and attachment, repressing flagellar operon, interfere with the DNA binding activities and phosphorylation events.

| Triterpenoids | Source | Organism | Source | Reference |
|---------------|--------|----------|--------|-----------|
| Isolimonic acid | *Citrus aurantium* L. | *V. harveyi* BB170 | | Vikram et al., 2011 |
| Ichangin | *Citrus aurantium* L. | *V. harveyi* BB120 | | Vikram et al., 2011 |
| Betulinic acids | Various species | *P. aeruginosa* PA14 | | Cho et al., 2013 |
| Ursolic acid | Various species | *P. aeruginosa* PAO1, *E. coli* JM109 |
| | | *V. harveyi* BB120 | | Ren et al., 2005 |
| Gymnemic acid | *Gymnemasylvestre* | *C. albicans* SC5314, *A. fumigates* | | Vediyappan et al., 2013 |

### Sulfur-containing compounds
**General mechanism of action:** Reacts with accessible cysteines in proteins and can inactivate essential enzymes, react with glutathione, shifts the cell redox potential to a more oxidized state and causes disulfide stress.

| Sulfur-containing compounds | Source | Reference |
|----------------------------|--------|-----------|
| Allicin | *Allium sativum* | *P. aeruginosa* PA14, |
| | | *S. epidermidis* | | Ta et al., 2014 |
| | | | | Pérez-Giraldo et al., 2003 |
| Ajoene | *Allium sativum* | *P. aeruginosa* lasB-gfp, |
| | | *E. coli* luxI-gfp | | Jakobsen et al., 2012 |
| Sulfuraphane | *Brassica* species | *P. aeruginosa* PA01, |
| | | *E. coli* DH5 | | Ganin et al., 2012 |
| Ally isothiocyanate | *Brassica* species | *L. monocytogenes*, *E. coli* |
| | | *C. violaceum* ATCC 1247 | | Borges, et al., 2013 |
| | | | | Borges et al., 2014 |
3.1 Preventing microbial adhesion

Various factors like pH, ionic strength, temperature, nutrients, genotype and phenotype of microorganism influence the process of adhesion. The bacterial adhesion mainly depends on the charge, hydrophobicity, presence of adhesion components (e.g., fimbriae, flagella and pili) and the EPS structure of microorganism (Donlan, 2002). The surface property of the material on which biofilm is formed, also plays an important role in its formation (Grossner et al., 2009). The hydrophobicity determines adhesion rate and experimentally the hydrophobicity or surface charge of microorganism is calculated as the zeta potential. It is defined as the mobility of the cell in the presence of an electric field under standard pH and temperature conditions (Ferreira et al., 2010; Palmer et al., 2007). The surface charge of the cells is often determined as its zeta potential, has been measured from the mobility of cells (Pratt and Kolter, 1998; Verstraeten et al., 2008). Hydrophobic surfaces have more negative value of hydrophobic attraction and hydrophilic surface tend to have positive hydrophobic attraction (Chaves and Da, 2004; Araújo et al., 2010). In most studies, it is found that hydrophobic, nonpolar surface like tetlon and other plastics, harbor more microbial adhesion than hydrophilic, polar surfaces like glass or metal (Fletcher and Loeb, 1979; Pringle and Fletcher, 1983; Bendiger et al., 1993). Stainless steel showed less bacterial load as compared to sandblast steel (Arnold and Bailey, 2000). Researchers have studied the effects of phenolic compounds on the change of cell surface charge with the some bacteria. Interaction of E. coli and S. aureus with phenolics (gallic and ferulic acids) reduces their negative charge (Abreu et al., 2013). The bacterial cells were treated with phenyl isothiocyanate and a significant change was observed in their hydrophobicity. The surface was made more hydrophilic (Abreu et al., 2013).

3.2 Control of cellular motility

Bacteria show various types of movements like swimming, swarming, gliding, etc., and these movements play an important role in biofilm formations. In case of swarming movement, the force generated by the motion overcomes the electrostatic force between the substratum and bacteria which help them in the initial attachments (Pratt and Kolter, 1998). Studies showed that a mutation in swarming controlling gene made it difficult for bacteria to form biofilm (Verstraeten et al., 2008; Inoue et al., 2008). The phytochemical, I-3-C decreased sliding and swimming movement whereas no effect was observed on bacterial swarming movement (Table 2). Varying results were observed by different phytochemicals on cellular motility during different duration of time. The swimming and swarming motility of P. aeruginosa, P. mirabilis and Serratia marcescens were decreased by methanolic extracts of Cuminum cyminum (Sybiya et al., 2012). However, cinnamaldehyde and eugenol from Cinnamomum cassia decreased the swimming motility of E. coli (Niu and Gilbert, 2004).

Table 2: Effect of various phytochemicals on modes of movement of microbes

| Phytochemicals                        | Micro-organisms              | Movements affected                  | References               |
|---------------------------------------|------------------------------|-------------------------------------|--------------------------|
| Indole-3-carbinol                     | E. coli, S. aureus           | Swimming, Sliding                   | Joana et al., 2014       |
| Salicylic acid                        | E. coli                      | Swimming                            | Joana et al., 2014       |
| Gallic acid and ferulic acid          | E. coli, P. aeruginosa, S. aureus, L. monocytogenes | Swimming, sliding                 | Borges et al., 2012     |
| Ferulic acid and Salicylic acid       | Bacillus cereus, P. fluorescens | Swimming                           | Borges et al., 2012; Lemos et al., 2014 |
| Allylisothiocyanate and 2phenylethylisothiocyanate | E. coli, P. aeruginosa, S. aureus, L. monocytogenes | Swimming, sliding                 | Borges et al., 2012     |
| Methyl eugenol (Cuminunccyminum)      | P. aeruginosa, P. mirabilis, Serratiamarcescens | swimming and swarming              | Sybiya et al., 2012      |
| Cinnamaldehyde and eugenol (Cinnamomum cassia) | E. coli                      | Swimming                            | Niu and Gilbert, 2004    |

3.3 Quorum sensing

QS plays an important role in the formation of biofilm (Xie et al., 2000). Cell-to-cell communication is dependent on synthesis of the inducer and their proper exchange and binding (Khan et al., 2009). Davies et al. (1998) performed an experiment on P. aeruginosa having two signaling pathways (lasR-lasI and rhlR-rhlI). The double mutants were used which did not produce any of the signal through which the biofilm was formed. This formed biofilm, lacked the typical biofilm architecture of a wild type, were thinner and cells were densely packed. Moreover, on simple surface treatment, these biofilms were easily removed (Davies et al., 1998). Quorum sensing inhibition (QSI) was performed on a biosensor strain Chromobacterium violaceum (CV12472), using the disc diffusion method (Borges et al., 2014). QSI was found to be dependent on phytochemical concentration. A clove oil compound, cinnamon, peppermint and lavender were identified having QS inhibitory
properties against C. violaceum (CV12472) (Khan et al., 2009; Zahin et al., 2010; Borges et al., 2014). Tecoma capensis, Sonchus oleraceus, Pityriasis alba, Pinus nigra, Jasminum sambac, Rosmarinus officinalis, Lavandula angustifolia and Laurus nobilis also act as a source of antimicrobial and QS inhibitors (Al-Hussaini and Mahasneh, 2009). Phytochemicals act on various target areas in order to bring out inhibitory effect on QS like inhibiting signal biosynthesis and acyl homoserine lactone synthase enzyme production and inhibiting the reception of signal molecules.

3.4 Change in bacterial static properties

The bacterial static property against phytochemicals proves to be helpful in controlling their effects when bacteria were found successful in forming a biofilm. The MIC and MBI values of phytochemicals were needed to be established (Chieu and John, 2015). The MIC and MBI values for Gram-negative bacteria is always greater than for Gram-positive bacteria (Vaara, 1992; Simões et al., 2008). The morphology of the E. coli and S. aureus cells in biofilm changed when observed after treatment with phytochemicals (essentials oils). The reduction in cell size, length and diameter was observed and the peptidoglycan structure of cell wall gets disrupted, cell contents leaks out and eventually leads to cell death (Chieu and John, 2015). Gallic (hydroxybenzoic acid), ferulic acids (hydroxy-cinnamic acid), hydroxycinnamic acid and hydroxybenzoic acid were also tested for their antimicrobial activities against E. coli and S. aureus (Borges et al., 2013).

4. Combined effects of phytochemicals and antibiotics

Phytochemicals act synergistically with antibiotics to overcome the problem posed by resistance strain. This combination even reduces the chances of side effects which are usually caused by use of antibiotics (Table 3). Many phytochemicals have been studied as resistance-modifying-agents (Abreu et al., 2013). The combinations of antibiotics (ciprofloxacin, tetracycline and erythromycin) with phytochemical (I-3-C, SP, SA and 7-HC) were tested for four different strains of S. aureus and three types of effects; synergistic, additive and antagonistic effect with antibiotics was observed (Joana et al., 2014). Many studies have been done on the combined effect of antibiotics and phytochemicals (LeBel, 1988; Simões et al., 2008; Saavedra et al., 2010; Biswas and Roymon, 2012; Abreu et al., 2013). The use of sesquiterpenoid, a phytochemical in combination of four antibiotics (ciprofloxacin, erythromycin, gentamicin and vancomycin), was found to increase the overall antimicrobial activity against E. coli and S. aureus (Simões et al., 2008). Further, an additive effect was observed when isothiocyanate and phenyl isothiocyanate were used with ciprofloxacin and erythromycin against S. aureus (Abreu et al., 2013). However, saponin with chloramphenicol showed synergistic behavior against E. coli (Biswa and Roymon, 2012).

Table 3: Effect of combinations of phytochemicals and antibiotics on S. aureus biofilm

| S. No. | Bacterial strains | Phytochemicals + Antibiotics |
|--------|------------------|------------------------------|
| **Synergistic effect** | | |
| 1. | S. aureus CECT 976 | Indole-3-carbinol + Tetracycline, Erythromycin, Ciprofloxacin |
| 2. | S. aureus XU212 | Indole-3-carbinol + Tetracycline, Saponin + Tetracycline, Salicylic acid + Tetracycline |
| 3. | S. aureus RN4220 | Indole-3-carbinol + Erythromycin, Saponin + Erythromycin, Salicylic acid + Erythromycin |
| 4. | S. aureus SA1199B | Indole-3-carbinol + Ciprofloxacin, Saponin + Ciprofloxacin, Salicylic acid + Ciprofloxacin |
| **Additive effect** | | |
| 1. | S. aureus CECT 976 | Saponin + Erythromycin |
| 2. | S. aureus XU212 | 7-Hydroxycoumarin + Tetracycline |
| **Antagonistic effect** | | |
| 1. | S. aureus CECT 976 | 7-Hydroxycoumarin + Erythromycin, Saponin + Tetracycline, Saponin + Ciprofloxacin |
| 2. | S. aureus RN4220 | 7-Hydroxycoumarin + Erythromycin |
5. Conclusion

Biofilm formation enables microorganism to endure situations such as immune defenses and conventional antimicrobial therapies. The biofilms are the dominant lifestyle of microorganisms in all environments, either natural or manmade and remain a serious concern in the healthcare, food and marine industries. This ability has challenged the treatment of infections caused by such microorganism. The development of effective strategies to combat biofilms is a challenging task. The rise of antibiotic resistance has led to a decrease in the efficacy of treatments for the elimination of biofilm infections. The researchers and clinicians have begun concentrating their efforts on coupling biofilm destruction with antimicrobial therapy as the increased tolerance of biofilm-embedded pathogens to antibiotics.

Phytochemicals represent a possible alternate for effective, inexpensive and safe antimicrobial agents. With the evolution of multiple drug resistant bacteria, there is always a need for new strategies to control them. The use of plant extract is very common in medicine since ancient times. The phytochemicals can be used in adjuvant or alone for control of infections as they are side-effect free. Phytochemicals have great ability to inhibit the bacterial quorum sensing system, therefore, reduce the bacterial pathogenesis. In recent time, the pharmacological effects of phytochemicals have been considered as a promising future antimicrobial drug for the management of infectious diseases. In the future, the active ingredients of more plants should be identified, purified and their antimicrobial role and the mechanism of action should be studied. Though, the phytochemicals have been considered as side-effect free but there are any adverse effects of these phytochemicals then it should also be studied on long term basis. The phytochemicals has a good future in treating deadly infectious diseases and may one day emerge as good adjuvant or substitute for conventional antibiotic therapies.

Future prospective

The major role of biofilm is in developing antimicrobial resistance, in chronic diseases and biofilm itself as a reservoir for pathogenic organism. Microbial biofilm research is proceeding on many fronts with particular emphasis on elucidation of the genes specifically expressed by biofilm-associated organism. More research is needed that should focus on the development of new methods of degradation of biofilms. The new approaches such as phytochemical treatments gaining more attentions that weaken the structure of the biofilm, and target every important component of biofilm. These seems to be better strategies for biofilm dispersal as it can more effectively release biofilm-associated microbes from the protection of the EPS. The reagents that can target the EPS on a molecular scale, or cause the microbes themselves to actively degrade their own biofilms, may represent the next logical step of targeting eradication of biofilm-avorded protection to infectious microorganisms. The phytochemicals demonstrated significant potential to reverse antibiotic resistance. However, in order to apply these phytochemicals with therapeutic/clinical purposes, further studies are required to ascertain their toxicity against mammalian cells and potential side effects.

Acknowledgements

The author, Kriti Kanwar gratefully acknowledges the Senior Research Fellowship from Indian Council of Medical Research, Govt. of India, New Delhi.

Conflict of interest

We declare that we have no conflict of interest.

Reference

Abreu, A.C.; Borges, A.; Simões, L.C.; Saavedra, M.J. and Simões, M. (2013). Antibacterial activity of phenyl isothiocyanate on Escherichia coli and Staphylococcus aureus. Medicinal Chem., 9:756-761.
Abreu, A.C.; Tavares, R.R.; Borges, A.; Mergulhão, F. and Simões, M. (2013). Current and emergent strategies for disinfection of hospital environments. J. Antimicrob. Chemother., 68:2718-2732.
Alekandra, T.; Grzegorz, F.; Mariusz, G and Joanna, N. (2012). Innovative strategies to overcome biofilm resistance. Bio. Med. Res. Int., 2013:1-13.
Al-Hussaini, R. and Mahasneh A.M. (2009). Microbial growth and quorum sensing antagonist activities of herbal plants extracts. Molecules, 14:3425-3435.
Almaradju, M.A.R. and Venkitanarayanan, K. (2011). Effect of transcinnamaldehyde on inhibition and inactivation of Cronobacter sakazakii biofilm on abiotic surfaces. J. Food Prot., 74:200-208.
Anwar, H.; Biesen, T.; Daugumpa, M.; Lam, K. and Costerton, J.W. (1989). Interaction of biofilm bacteria with antibiotics in a novel in vitro chemostat system. Antimicrob. Agents Chemother., 33:1824-1826.
Anwar, H.; Strip, J.L. and Costerton, J.W. (1992). Susceptibility of biofilm cells of Pseudomonas aeruginosa to bactericidal actions of whole blood and serum. FEMS Microbiol. Lett., 92:235-242.
Araújo, E.A.; Andrade, N.J.; Carvalho, A.F; Ramos, A.M.; Silva, C.A.S. and Silva, I.H.M. (2010). da Aspectoscoloidais da adesão de micro-organismos. Quim. Nova., 33:1940-1948.
Arnold, J.W. and Bailey, G.W. (2000). Surface finishes on stainless steel reduce bacterial attachment and early biofilm formation: Scanning electron and atomic force microscopy study. Poultry Sci., 79:1839-1845.
Bakkiyaraj, D.; Nandhini, J.R.; Malathy, B. and Pandian, S.K. (2013). The antibiofilm potential of pomegranate (Punica granatum L.) extract against human bacterial and fungal pathogens. Biofuel., 29:929-937.
Bendinger, B.; Rijnaarts, H.H.M.; Altendorf, K. and Zehnder, A.J.B. (1993). Physicochemical cell surface and adhesive properties of coryneform bacteria related to the presence and chain length of mycolic acids. App. Environ. Microbiol., 59:3973-3977.
Biedlingmaier, J.F.; Samaranayake, R. and Whelan, P. (1998). Resistance to biofilm formation on otologic implant materials. Otolaryngol. Head Neck Surg., 118:444-451.
Biswas, D. and Roymon, M.G. (2012). Validation of antibacterial activity of saponin against diarrheagenic E. coli isolated from leaves and bark of Acacia arabica. J. Phytol., 4:21-23.
Borges, A.; Ferreira, C.; Saavedra, M.J. and Simões, M. (2013). Antibacterial activity and mode of action of ferulic and gallic acids against pathogenic bacteria. Microb. Drug Resistance, 19:256-265.
Borges, A.; Saavedra, M.J. and Simões, M. (2012). The activity of ferulic and gallic acids in biofilm prevention and control of pathogenic bacteria. Biofouling, 28:755-767.
Borges, A.; Serra, S.; Abreu, A.C.; Saavedra, M.J.; Salgado, A. and Simões, M. (2014). Evaluation of the effects of selected phytochemicals on quorum sensing inhibition and in vitro cytotoxicity. Biofouling, 30:183-195.
Borges, A.; Simões, I.; Serra, C.; Saavedra, M. and Simões, M. (2013). Activity of allylisothiocyanate and 2-phenylethylisothiocyanate on motility and biofilm prevention of pathogenic bacteria. In: Méndez-Vilas, E. (ed.) Worldwide research efforts in the fighting against microbial pathogens: from basic research to technological developments; Brown Walker Press.; Boca Raton, FL, USA. pp:8-12.

Brackman, G.; Defoirdt, T.; Miyamoto, C.; Bossier, P.; Calenbergh, S.; Nelis, H. and Coenye, T. (2008). Cinnamaldehyde and cinnamaldehyde derivatives reduce virulence in Vibrio spp. by decreasing the DNA-binding activity of the quorum sensing response regulator LuxR. BMC Microbiol., 16:149. doi: 10.1186/1471-2180-8-149.

Byarugaba, D.K. (2004). A view on antimicrobial resistance in developing countries and responsible risk factors. Int. J. Antimicrob. Agents, 24:105-110.

Cartagena, E.; Colom,O.A.; Neske, A.; Valdez, J.C. and Bardeón, A. (2007). Effects of plant lactones on the production of biofilm of Pseudomonas aeruginosa. Chemical Pharmaceutical. Bull., 55:22-25.

Chaves, L. and Da C.D. (2004). Estudo da cinética de formação de biofilmes na superfície do contato com águas potáveis. Universidade do Minho: Braga, Portugal. (In Portuguese) http://hdl.handle.net/1822/95

Chesney, P.J. (1994). Infections of the female genital tract. In: Bisno, A.L. and Waldvogel, F.A. (eds.) Infections associated with prosthetic valves. American Society of Microbiology, New York. pp:374-377.

Chieu, A.K.T. and John, T.A. (2015). Mini review of phytochemicals and plant taxa with activity as microbial biofilm and quorum sensing inhibitors. Molecules, 21:1-26.

Cho, H.S.; Lee, J.; Ryu, S.Y.; Joo, S.W.; Cho, M.H. and Lee, J. (2013). Inhibition of Pseudomonas aeruginosa and Escherichia coli O157: H7 biofilm formation by plant metabolite 3-phenylindoline. J. Agric. Food Chem., 61:7120-7126.

Cochrane, D.M.G.; Brown, M.R.W.; Anwar, H.; Wellar, P.H.; Lam, K. and Costerton, J.W. (1996). Antibody response to Pseudomonas aeruginosa surface protein antigens in a rat model of chronic lung infection. J. Medical Microbiol., 27:255-261.

Coenye, T.; Brackman, G.; Rigole, P.D.W.E.; Honraet, K.; Rossel, B. and Nelis, H.J. (2012). Eradication of Propionibacterium acnes biofilms by plant extracts and putative identification of 3,4-cis-estradiol and salisodiol as active compounds. Phytomedicine, 19:409-412.

Costerton, J.W.; Stewart, P.S. and Greenberg, E.P. (1999). Bacterial biofilms: A common cause of persistent infections. Science, 284:1318-1322.

Dang, R. (2018). Role of antinutrient metabolites of plant on production of secondary metabolites and human health. Ann. Phytochem., 7(1):1-4.

Dart, J.K.G. (1996). Contact lens and prosthesis infections. In: Tasman and Jaeger E.A. (eds.) Duane’s foundations of clinical ophthalmology. Lippincott-Raven, Philadelphia, pp:1-30.

Davies, D.G.; Parsek, M.R.; Pearson, J.P.; Iglewski, B.H.; Costerton, J.W. and Greenberg, E.P. (1998). The involvement of cell-to-cell signals in the development of a bacterial biofilm. Science, 280:295-298.

De-Beer, D.; Stooldy, P.; Roe, F. and Lewandowski, Z. (1994). Effects of biofilm structure on oxygen distribution and mass transport. Biotechnol. Bioengg., 43:1131-1138.

Dominque, G.J. and Hellstrom, W.J.G. (1998). Prostataitis. Clinic Microbiol. Rev., 11:604-613.

Donelli, G. and Francolini, I. (2001). Efficacy of antihemostatic, antibiotic and antiseptic coatings in preventing catheter related infections: Review. J. Chemother., 13:595-606.

Donlan, R.M. and Costerton, J.W. (2002). Biofilms: Survival mechanisms of clinically relevant microorganisms. Clin. Microbiol. Rev., 15:167-193.

Douglas, J.L. and Cobbs, C.G. (1992). Prosthetic valve endocarditis. In: Kaye, D. (ed.) Infective endocarditis, 2nd ed. Raven Press, New York, pp:375-396.

Dürig, A.; Koukounoumaki, I.; Veijborg, R.M. and Klemm, P. (2010). Chemoinformatics-assisted development of new anti-biofilm compounds. Appl. Microbiol. Biotechnol., 87:309-317.

Elliott, T.S.J.; Moss, H.A.; Tebbo, S.E.; Wilson, L.C. and Bonser, R.H. (1997). Novel Approach to Investigate a Source of Microbiol Contamination of Central Venous Catheters. Eur. J. Clin. Microbiol. Infect. Dis., 16:210-213.

Espeland, E.M. and Wetzel, R.G. (2001). Complexation, stabilization and UV photolysis of extracellular and surface-bound glucosidase and alkaline phosphatase: Implications for biofilm microbiota. Microbiol. Ecol., 42:572-585.

Fahim, M.; Shrivastava, B.; Shrivastava, A.K.; Ibrahim, M.; R. Parveen, R. and Ahmad, S. (2017). Review on extraction methods, antioxidant and antimicrobial properties of volatile oils. Ann. Phytomed., 6:3-46.

Ferreira, C.; Romsaninho, R.; Simões, M.; Pereira, M.C.; Bastos, M.M.; Nunes, O.C.; Coelho, M. and Melo, L.F. (2010). Biofilm control with new microparticles carrying a biocide. Biofouling., 26:205-212.

Fleming, D.; Chahin, L. and Rumbaugh, K. (2017). Glycose hydrolases degrade polymicrobial bacterial biofilms in wounds. Antimicrob. Agents Chemotherapy, 61:1-16. doi:10.1128/AAC.01998-16.

Fletcher, M. and Loeb, G.L. (1979). Influence of substrate characteristics on the attachment of a marine pseudomona to solid surfaces. App. Environ. Microbiol., 37:67-72.

Ganin, H.; Rayo, J.; Amara, N.; Levy, N.; Krief, P. and Meijler, M.M. (2012). Sterilization and erucin, Natural isothiocyanates from Broccoli, Inhibit Bacterial Quorum Sensing. Med. Chem. Commun., 4:175-179.

Garg, S. and Armi, W. (2017). Role of naturally occurring phytochemicals in overcoming the pathogenicity of Pseudomonas aeruginosa. Ann. Phytomed., 6:47-54.

Govan, J.R.W. and Deretic, V. (1996). Microbial pathogenesis in cystic fibrosis: Mucoad Pseudomonas aeruginosa and Burkholderia cepacia. Microbiological Rev., 60:539-574.

Grossner-Schreiber, B.; Teichmann, J.; Hannig, M.; Dorfer, C.; Wenderoth, D.F. and Ott S.J. (2009). Modified implant surfaces show different biofilm compositions under in vivo conditions. Clin. Oral Implants Res., 20:817-826.

Gupta, P.; Sarkar, S.; Das, B.; Bhattacharjee, S. and Tribedi, P. (2016). Biofilm, pathogenesis and prevention—a journey to break the wall: A review. Arch. Microbiol., 198:1-15.

Hall, S.L.; Costerton, J.W. and Stookey, P. (2004). Bacterial biofilms: From the natural environment to infectious diseases. Nat. Rev. Microbiol., 2:95-108.

Hancock, E.W.; Schlant, R.W.; Alexander, R.A.; Rouke, O.; Roberts, R. and Sonnenblick, E.H. (1994). Artificial valve disease. In: Alexander, R.W., Schlant, R.C. and Fuster, V. (eds.) The heart arteries and veins. 8th ed. vol. 2. New York:McGraw-Hill, Health Professions Division, NY, pp:1539-1545.

Hengzhuang, W.; Wu, H.; Cifuo, O.; Song, Z. and Holby, N. (2011). Pharmacokinetics/pharmacodynamics of colistin and imipenem on mucoid and nonmucoid Pseudomonas aeruginosa biofilms. Antimicrob. Agents Chemother., 55:4469-4474.

Ho-Sui, S.J.; Fedynak, A.; Hsiao, W.W.; Langille, M.G. and Brinkman, F.S. (2009). The association of virulence factors with genomic islands. Nucleic Acids Res., 4:80-94.
Biofilm formation by inhibiting sortase activity. Arch. Oral Biol., 58:1343-1348.

Krause, P.J.; Owens, N.J.; Nightingale, C.H.; Klinke, J.J.; Lehmann, W.B. and Quintiliani, R. (1982). Penetration of amoxicillin, cefaclor, erythromycin-sulfisoxazole, and trimethoprim-sulfamethoxazole into the middle ear fluid of patients with chronic serous otitis media. J. Infectious Disease, 145:815-821.

Kumar, A.; Alam, A.; Rani, M.; Elhesham, N.Z. and Hasnain, S.E. (2017). Biofilms: Survival and defense strategy for pathogens. Int. J. Medical Microbiol., 307:481-489.

Kuzma, L.; Rózalski, M.; Walencza, E.; Rózalska, B. and Wysokinska, H. (2007). Antimicrobial activity of diterpenoids from hairy roots of Salvia scarea L.: Salviposine as a potential anti-biofilm agent active against antibiotic resistant Staphylococcus. Phytomedicine, 14:31-35.

Punicalagin inhibits biofilm formation by inhibiting Strepococcus mutans biofilm formation by inhibiting sortase activity. Arch. Oral Biol., 58:1343-1348.

Krause, P.J.; Owens, N.J.; Nightingale, C.H.; Klinke, J.J.; Lehmann, W.B. and Quintiliani, R. (1982). Penetration of amoxicillin, cefaclor, erythromycin-sulfisoxazole, and trimethoprim-sulfamethoxazole into the middle ear fluid of patients with chronic serous otitis media. J. Infectious Disease, 145:815-821.

Kumar, A.; Alam, A.; Rani, M.; Elhesham, N.Z. and Hasnain, S.E. (2017). Biofilms: Survival and defense strategy for pathogens. Int. J. Medical Microbiol., 307:481-489.

Kuzma, L.; Rózalski, M.; Walencza, E.; Rózalska, B. and Wysokinska, H. (2007). Antimicrobial activity of diterpenoids from hairy roots of Salvia scarea L.: Salviposine as a potential anti-biofilm agent active against antibiotic resistant Staphylococcus. Phytomedicine, 14:31-35.
Sharma, G.; Raturi, K.; Dang, S.; Gupta, S. and Gabrani, R. (2014). Combinatorial antimicrobial effect of curcumin with selected phytochemicals on Staphylococcus epidermidis. 1. Asian Natural Product Res., 16:535-541.

Shayeeg, S., Rasooli, I.; Taghizadeh, M. and Astaneh, S.D. (2008). Phytotherapeutic inhibition of supragingival dental plaque. Natural Product Res., 22:428-439.

Simões, M.; Rocha, S.; Coimbra, M.A. and Vieira, M.J. (2008). Enhancement of Escherichia coli and Staphylococcus aureus antibiotic susceptibility using sesquiterpenoids. Medicinal Chem., 4:616-623.

Singh, R.; Ray, P.; Das, A. and Sharma, M. (2010). Penetration of antibiotics through Staphylococcus aureus and Staphylococcus epidermidis biofilms. J. Antimicrobiol. Chemother., 65:1955-1958.

Somya, E.A.; Sand, I.K.; Hasun, L.; Ghidane, Z.; Hind, M. and Adnane, R. (2011). Carvacrol and thymol components inhibiting Pseudomonas aeruginosa adherence and biofilm formation. Afr. J. Microbiol., 5:3229-3232.

Stapleton, F. and Dart, J. (1995). Pseudomonas aeruginosa associated with biofilm formation on a disposible soft contact lens. Br. J. Ophthalmol., 79:864-865.

Stapleton, F.; Dart, J.K.; Matheson, M. and Woodward, E.G. (1993). Bacterial adherence and glycolcalyx formation on unworn hydrogelenses. J. Br. Contact Lens Assoc., 16:113-117.

Stickler, D.; Ganderton, I.; King, J.; Netleton, J. and Winters, C. (1993). Proteus mirabilis biofilms and the encrustation of urethral catheters. Urol. Res., 21:407-411.

Stickler, D.J. (1996). Bacterial biofilms and the encrustation of urethral catheters. Biofouling, 9:293-305.

Stickler, D.J.; King, J.; Netleton, J. and Winters, C. (1993). The structure of urinary catheter encrusting biofilm cells. Cells Mater., 3:315-319.

Sibyria, V.P.L.A.; Agilandeswari, P.; Musthafa, K.S.; Karutha, P.S. and Verra, R.A. (2012). Antibiofilm and quorum sensing inhibitory potential of Cuminum cyminum and its secondary metabolite methyl eugenol against Gram-negative bacterial pathogens. Food Res. Int., 45:85-92.

Ta, C.A.; Freundorfer, M.; Mah, T.F.; Oatmeal-Rojas, M.; Garcia, M.; Sanchez-Vindas, P.; Poveda, L.; Masche, J.A.; Baker, B.J.; Adonizito, A.L.; Downum, K.; Durst, T. and Arnaison, J.T. (2014). Inhibition of bacterial quorum sensing and biofilm formation by extracts of neotropical rainforest plants. Planta Medica, 80:343-350.

Teitzel, G.M. and Parsch, M.R. (2003). Heavy metal resistance of biofilm and planktonic Pseudomonas aeruginosa. Appl. Environ. Microb., 69:2313-2320.

Totani, T.; Nishinou, Y.; Tateishi, Y.; Yoshida, Y.; Kitakata, H.; Niki, M.; Kaneko, Y. and Matsumoto, S. (2017). Effects of nutritional and ambient oxygen condition on biofilm formation in Mycobacterium avium subsp. hominisuis via altered glycolipid expression. Sci. Rep., 7: 41775. doi: 10.1038/srep41775.

Tunkel, A.R. and Mandell, G.L. (1992). Infecting microorganisms. In: Kaye D. (ed) Infective endocarditis. 2nd ed. Raven Press, NewYork, pp: 85-97.

Upadhyay, A.; Upadhyaya, I.; Kollanoor-Johny, A. and Venkitanarayanan, K. (2013). Antibiofilm effect of plant derived antimicrobials on Listeria monocytogenes. Food Microbiol., 36:79-89.

Vaara, M. (1992). Agents that increase the permeability of the outer membrane. Microbiological Rev., 56:395-411.

Vediappan, G.; Dumontet, N.; Pelisier, F. and D’Enfert, C. (2013). Gymnemic acids inhibit hyphal growth and virulence in Candida albicans. PLoS ONE, 8:e74189.

Verstraeten, N.; Brucken, K.; Dehkmami, B.; Fauvart, M.; Fransaer, J.; Vermant, J. and Michiels, J. (2008). Living on a surface: swarming and biofilm formation. Trends Microbiol., 16:496-506.

Vikram, A.; Jesudhasan, P.R.; Jayaaprakash, G.K.; Pillai, S.D. and Patil, B.S. (2011). Citrus limonoids interfere with Vibrio harveyi cell-cell signalling and biofilm formation by modulating the response regulator LuxO. Microbiol., 157:99-110.

Vlcheze, C.; Hartman, T.; Weinrich, B.; Jain, P.; Weisbod, T.R.; Leung L.W.; Freundlich, J.S. and Jacobs, W.R. (2017). Enhanced respiration prevents drug tolerance and drug resistance in Mycobacterium tuberculosis. Proceedings Nat. Acad. Sci. USA., 114:4495-4500.

Walencka, E.; Rozalska, S.; Wysokinika, H.; Rozalski, M.; Kuzma, L. and Rozalska, B. (2007). Saliviposine and aethiopinone from Salvia sclarea hairy roots modulate staphylococcal antibiotic resistance and express anti-biofilm activity. Planta Medica, 73:545-551.

West, S.A.; Griffin, A.S.; Gardner, A. and Diggle, S.P. (2006). Social evolution theory for microorganisms. Nat. Rev. Microb., 4:597-607.

Wilson, I.A.; Sawant, A.D. and Ahearne, D.G. (1991). Comparative efficacies of soft contact lens disinfectant solutions against microbial films in lens cases. Arch. Ophthalmol., 109:1155-1157.

Wolf, A.S. and Kreiger, D. (1986). Bacterial colonization of intrauterine devices (IUDs). Arch. Gynecol., 239:31-37.

Wu, H.; Moser, C.; Wang, H.Z.; Holby, N. and Song, Z.J. (2015). Strategies for combating bacterial biofilm infections. Int. J. Oral Sci., 7:1-7.

Xie, H.; Cook, G.S.; Costerton, J.W.; Bruce, G.; Rose, T.M. and Lamont, R.J. (2000). Intergeneric communication in dental plaque biofilms. J. Bacteriol., 182:7067-7079.

Xu, K.D.; McFeters, G.A. and Stewart, P.S. (2000). Biofilm resistance to antimicrobial agents. Microbiol., 146:547-549.

Yasuda, H.; Aji, Y.; Koga, T.; Kawada, H. and Yokota, T. (1993). Interaction between biofilms formed by Pseudomonas aeruginosa and clarithromycin. Antimicrob. Agents Chemother., 37:1749-1755.

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

Zhang, Y. (2014). Persists, persistent infections and the Yin-Yang model. Emerging Microbes Infecc., 3: doi:10.1038/emi.2014.3.

Zhou, L.; Zheng, H.; Tang, Y.; Yu, W. and Gong, Q. (2013). Eugenol inhibits quorum sensing at sub-inhibitory concentrations. Biotechnol. Lett., 35:631-637.