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REVIEW

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A narrative review on bacterial biofilm: its formation, clinical aspects and inhibition strategies

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Abstract

Background The predominant mode of life of most of the bacteria is their biofilm state. Based on the type of bacteria existing within the biofilm, it might be beneficial or harmful. Its beneficial aspects have been exploited mostly in waste management strategies. These biofilms affected the food industry, dairy industry and oil industry, causing huge losses by food spoilage, reduced heat transfer efficiencies and corrosion caused by biofilms in pipelines. They were considered a crucial risk to human well-being. Biofilms were responsible for more than 75% of the clinical infections caused in humans.

The main body of the abstract Biofilms are multimicrobial complex structures that are resistant to antibiotics and stressful environments. The biofilm stage may provide various advantages to the bacteria during bacterial infections in human beings. The extracellular polymeric substances hold the bacterial community colonized in the biofilm. The bacteria within the biofilm are more resistant to antibiotics, whereas the planktonic bacteria are susceptible to them. Quorum sensing regulated biofilm formation, which can be manipulated to eradicate devastating effects caused by biofilms. The occurrence of biofilm on the clinical devices leads to the malfunction of the implants and complicates the patients' health conditions. Biofilms also cause non-device-associated health problems. The major anti-biofilm strategies are the utilization of enzymatic activity and hindrance of quorum sensing. The auto-inducers, which play a major role in quorum sensing, are mimicked by inhibitors. This prevents the binding of auto-inducers to the receptors, eventually leading to blockage of biofilm formation.

Short conclusion The significant background knowledge regarding the biofilm, its formation, clinical aspects and inhibition strategies has been highlighted in this review. This information dissipated anticipates new applications of plant compounds as an alternative to antibiotics, since they may act as anti-quorum sensing molecules. For instance, inhibitory compounds like Linalool and eugenol from the essential oil of different plants displayed antibiofilm activity against biofilms formed by *Streptococcus pyogenes* and *Porphyromonas gingivalis*, respectively. Further research is required to exploit the inhibitory properties of the various other bioactive compounds present in plant extract, and thereby, we can protect human beings from several device and non-device-related infections caused by biofilms such as catheter-related bloodstream infections, tuberculosis, cystic fibrosis, chronic obstructive pulmonary diseases, dental caries and periodontitis.

Keywords Biofilm, Bacteria, Extracellular polymeric substance, Quorum sensing, Quorum quenching, Colonization

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Background

Biofilms are defined as a well-organized, multimicrobial three-dimensional community composed of a group of microorganisms encased within self-produced polymeric matrix, adhered to each other on biotic or abiotic surfaces. Initially, a small group of cells or a single cell divides and differentiates into a so-called complex structure [1]. The bacterial population within the biofilm can be homogenous or heterogeneous. Even though biofilms are frequently perceived as potentially harmful for the clinical and various other industrial domains, many biofilms are beneficial, and there are numerous reports about the beneficial use of these biofilms [2]. Beneficial biofilms have a variety of uses in agricultural, medical, environmental, food and other fields, including biofertilizer, antibacterial, antimicrobial agents, filtration, corrosion prevention, wastewater treatment biofouling, microbial fuel cells, bioremediation and food fermentation [2–4]. In cheese manufacturing, raw milk and Tina biofilm are the sources of the fermentative microflora which includes bacteria such as *Lactobacillus lactis*, *Streptococcus thermophiles*, *Enterococcus faecium* and *Lactobacillus delbrueckii* [5]. The primary bacteria that promote plant growth are *Bacillus*, *Rhizobium*, *Acinetobacter*, *Enterobacter*, *Alcaligenes*, *Azospirillum*, *Burkholderia*, *Arthrobacter*, *Erwinia*, *Azotobacter*, *Flavobacterium*, *Serratia* and *Beijerinckia* [6]. For a very long time, biofilms have been used successfully in the production of vinegar. Vinegar was produced on free-floating wood chips by *Acetobacter* or *Gluconobacter* with a higher output, which promotes the proliferation of vinegar bacteria [7].

Bioremediation is a method of pollution control in which various contaminants are destroyed or changed into less harmful forms. In bioremediation, microorganisms are used to break down environmental pollutants like plastic wastes, toxic heavy metals, synthetic dyes and other toxic compounds. Protection of the environment and human health depends on the bioremediation process [8]. Synthetic wastewater containing 2,4-dichlorophenol was degraded by *P. putida*, supplemented to the biofilm reactor with activated microbial sludge culture [9]. Alkanes, pesticides, polyaromatic substances and hydrocarbons can be broken down by aerobic microorganisms like *Pseudomonas*, *Rhodococcus*, *Alcaligenes*, *Mycobacterium* and *Sphingomonas*, and they use these pollutants to meet their needs for carbon sources and energy. In river sediments, anaerobic bacteria are used to break down polychlorinated biphenyls and dechlorinate the solvents trichloroethylene and chloroform [8]. The emergence and endurance of biofilms in the human body lead to the occurrence of above 75% of microbial infections, by the National Institutes of Health. Some bacterial biofilms have both functional and defensive roles, such as the gut microbiota [10]. Homeostasis has been maintained by interactions between the beneficial bacteria inside the intestine and the intestinal epithelium [11]. Dysbiosis is a state of imbalance in the microbiota, which is also related to various diseases [12].

Biofilms formed by bacteria play various roles in industries and are widely dispersed. In the dairy industry, equipment impairment and food spoilage caused by biofilms lead to economic loss for the industry as well as cause major hygienic problems (Fig. 1) [13]. Heat transfer efficiencies of the pipelines and heat exchangers can be reduced if a suitably thick layer of biofilms is formed; whereas corrosion in pipelines and tanks is caused by the biological and chemical reactions catalysed by the microbes present in the biofilms [14, 15]. Several bacterial populations producing biofilms display resistance against antibiotics [16]. The structure of the biofilms has been modulated to enable the bacteria to survive in different stressful environments [17]. The survival of single-celled organisms in adverse conditions has been facilitated by "group behaviour", which is due to the biofilm that safeguards and promotes these organisms to lead a multicellular lifestyle [18]. On liquid surfaces, the biofilms are found to be seen as a floating mat and the biofilms are also found in submerged conditions [19]. Since the biofilms have diverse structural elements, both undifferentiated flat biofilms, as well as mushroom-like tall biofilms with distinct water channels, have been visualized, according to the type of bacteria responsible for their formation [20, 21].

EPS are extracellular polymeric substances on which the bacterial communities are lodged. Polysaccharides are the main biomolecules present in EPS and it also consists of lipids, proteins and nucleic acids [23]. The

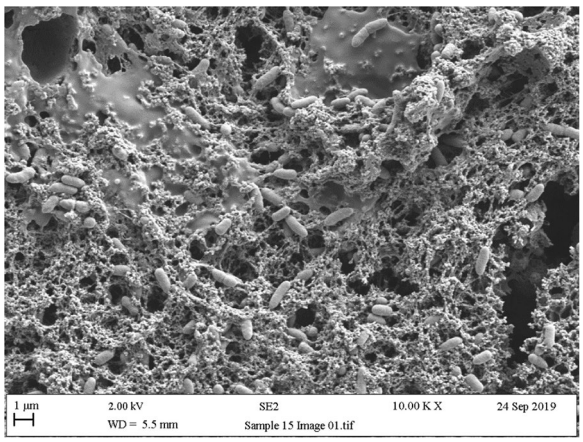


Fig. 1 Scanning electronic microscopy image of stainless steel of 3-day biofilms formed by *Pseudomonas fluorescens*. ©Carrascosa C et al. [22]

bacterial community prevailing in the biofilm are held together by the scaffold formed by lipids, lipopolysaccharides and glycopeptides, which are polymers. The formation and stabilization of biofilms require cell-to-surface interactions and also interactions between the cells. This is mediated by bacterial polysaccharides [24]. It was discovered that viscoelastic behaviour, which helps to resist mechanical stress, is displayed by the biofilms and it was also revealed that they are hydrogels [25]. The water and nutrients are trapped in the matrix of EPS, which is used by the bacteria for its existence. Inside the matrix of EPS, the water is efficiently captured by its hydrogen bonding with the hydrophilic polysaccharides within the EPS [18]. Conceptual framework of the functions of microbial extracellular polymeric substances (EPS) in soil is depicted in Fig. 2

Biofilms aid the bacteria to thrive in the environment by increasing their attachment to different surfaces; protecting them from desiccation, antibiotics, predation, immune attack and starvation. All these properties prevailing in the biofilms provide bacterial fitness to the concerned bacteria [27, 28]. Biofilm formation is regulated by quorum sensing; in addition to this quorum sensing also regulates spore formation and the production of secondary metabolites [29, 30]. Bacterial cell-to-cell communication is synchronously called quorum sensing, in which they communicate through autoinducers (signalling molecules) in a density-dependent manner; it aids the coordination of the bacterial colony to exist as a sole component [31–33].

Main text

Types of biofilms

Based on the type of bacteria present in the biofilm, they are two types: Gram-positive biofilm and Gram-negative biofilm. On the cell walls of Gram-positive bacteria, teichoic acid (TA) is found, whereas in Gram-negative bacteria there is the presence of lipopolysaccharides (LPS). These components supply charges to the bacterial outer surface, which may also be responsible for the adherence to the surfaces and also in biofilm formation [34, 35]. The adhesion of the Gram-negative bacteria to the surface and their progression to biofilm formation is determined by the length of LPS and its dissimilarity in various parts of the bacteria [35]. Colonization of bacteria is influenced by teichoic acid in the case of Gram-positive bacteria and the case of Gram-negative bacteria, it is lipopolysaccharide that plays the role [36]. Cell wall teichoic acid present in *Staphylococcus aureus* plays a role in bacterial colonization on natural surfaces like nasal tissues and also on heart valve prostheses or catheters, which are artificial surfaces [34].

Cell wall surfaces appear to be a notable and precise target for anti-biofilm approaches since the surface of the cell wall governs the surface properties of two types of bacteria [37]. Both the Gram-type bacteria have flagella that helped them to move and are attached to the

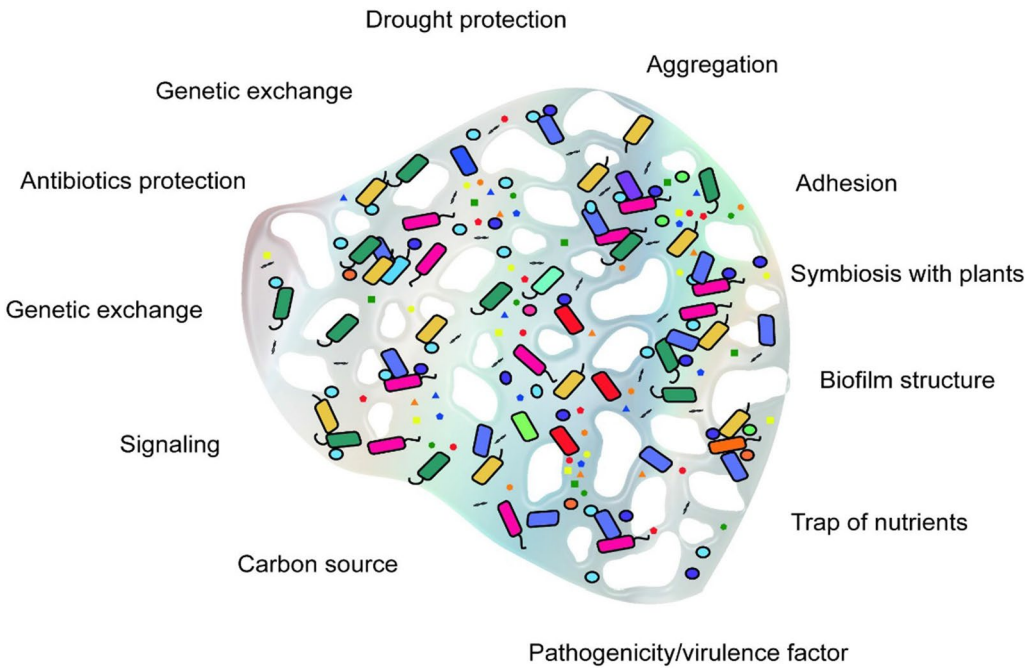


Fig. 2 Conceptual framework of the functions of microbial extracellular polymeric substances (EPS) in soil. ©Costa OYA et al. [26]

surface through polysaccharide secretion [38]. The Gram-positive flagellated bacteria (*Bacillus subtilis*) show attachment to surfaces through the exopolysaccharide formation, and its flagellar expressions are downregulated [39, 40], whereas its non-flagellated type (*S. aureus*) show Brownian motion since it has no organ for motility to reach the target surfaces [37]. The chemical nature of the quorum-sensing molecules varies by the production of AIP (autoinducing peptides) in Gram-positive bacteria and AHL (acyl-homoserine lactones) in Gram-negative bacteria [33]. Autoinducers-2 (AI-2) are non-species-specific and affect both Gram-positive and Gram-negative bacteria [41].

Mechanism of biofilm formation

There are four prominent phases in the sequential process of biofilm formation: (i) migration of cells and its adherence to the surface, (ii) micro-colony formation and EPS (extracellular polymeric substance) exudation from cells; irreversible attachment resulting in cell proliferation and formation of matrix, (iii) maturation stage, (iv) cell detachment [42]. The different stages of biofilms are represented in Fig. 3. Each of these steps is described below.

Migration and adherence

In *S. aureus*, the initiation of biofilm happens when the floating cells are adhered to by the hydrophilic or hydrophobic interaction between the available surface and cell surface [43, 44]. The interaction of bacteria on the surface is strengthened by bacterial appendages like flagella, pili and fimbriae. This strengthening is due to the hydrophobic force on the surface, which causes the reduction of the repulsive force between the bacterial cell surface and the living or non-living surface [45]. Other than these forces, certain proteins also play a major role in mediating the binding between them. Heilmann and co-workers [46] first described such specific proteins, autolysins, which possess dual roles: adhesive and enzymatic function [47]. To bind to biotic surfaces, the cells produce certain CWA (Cell Wall-anchored) proteins. Among these MSCRAMMs (Microbial surface components recognizing adhesive matrix molecules) are the well-distinguished group [48]. A small amount of exopolymeric material is produced in the initial stage and the bacterial cells are encased in it [1].

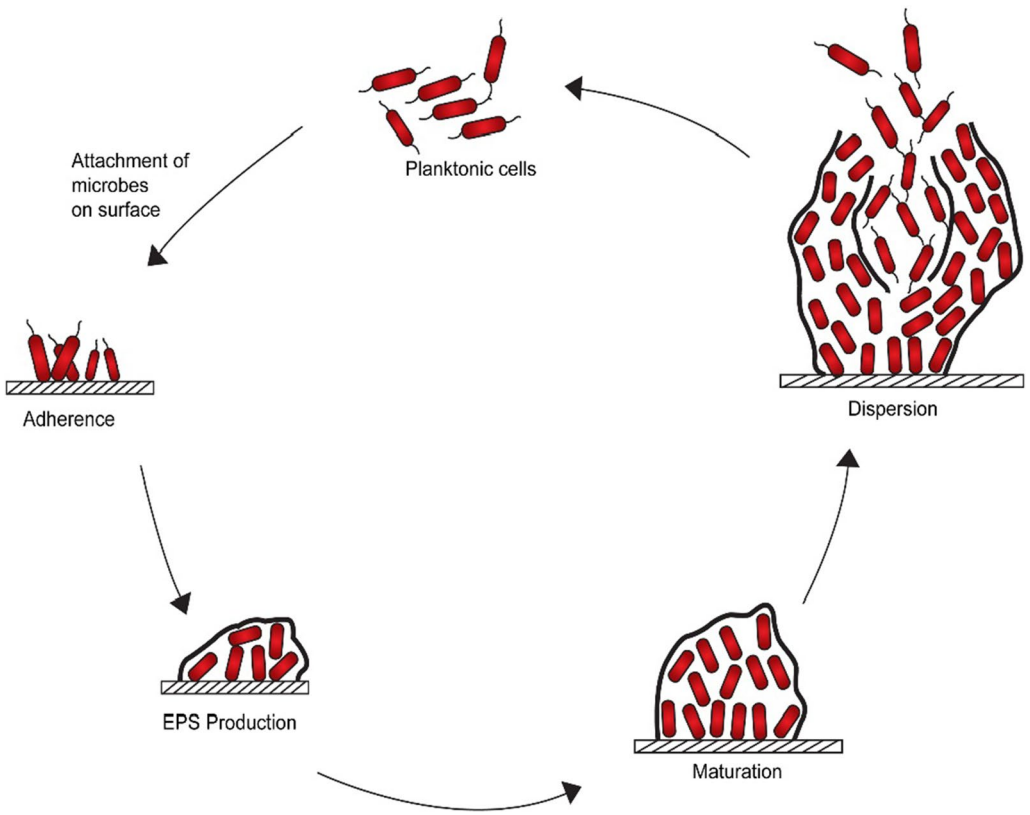


Fig. 3 Mechanism of biofilm formation

Micro-colony formation and EPS

The bacteria attached to the surface proliferate and form micro-colonies. Different types of micro-communities are present in a biofilm. Metabolic product distribution, exchange of substrates and excretion are facilitated by coordination among the micro-colonies [49]. Constituents present in a bacterial matrix vary depending on the environmental conditions, different bacterial species and their strain types [50, 51]. The extracellular polymeric substance released by the cells contains polysaccharides, nucleic acids (eDNA), lipids and proteins [52]. This complex mixture is not only involved in structural support but also has a role in fetching nutrients and providing protection against antimicrobial agents and immune responses [53].

Maturation stage

Due to a change in microbial cell density, certain signalling molecules called auto-inducers are produced by these microbial cells. These auto-inducers play a vital role in quorum sensing (QS), the bacterial cell's capability to sense the cell density through cell-to-cell communication. When a minimum threshold is attained, these signalling molecules induce alteration of gene expression [54]. The binding of the auto-inducer to the receptor causes the target genes to either be activated or repressed. Owing to this modification of the quorum sensing, the whole bacterial community in the biofilm benefits by exhibiting a combined response. This unified nature of the response is obtained by maintaining an ideal size of biofilm and synchronizing virulence phenotypes [55]. The integrated response of the bacteria enables it to act similarly to a multicellular organism, so it has the adaptation to live in a changing environment. In addition to managing bacterial population density, QS also assists the transfer of beneficial mutations among the colony, which provides tolerance to antibiotics and improves nutrient accessibility [56]. During the maturation stage, due to the action of auto-inducers, aggregation occurs between the bacterial cells by the secretion of EPS. A three-dimensional architecture is obtained by the biofilm and EPS is a prominent material responsible for this community. Voids are produced interstitially in the matrix and these structures act as channels which contain water. Nutrients are distributed and waste products are removed from the micro-colonies through this channel that also functions as a circulatory system [57].

Cell detachment

After completing the maturation, the cells in the biofilm produce certain chemicals and EPS lysing enzymes that degrade the matrix and help in the dispersion of the biofilm [18]. For this process of detachment, the cell communities within the biofilm use different degrading enzymes, for example, alginate lyase produced by *Pseudomonas aeruginosa* and *P. fluorescens*, hyaluronidase by *Streptococcus equi* and N-acetyl-heparosan lyase by *Escherichia coli* [58, 59]. Bacterial movement requires flagella. Therefore, protein expression of genes for flagella formation is upregulated and this allows the free locomotion of the organism, so that sessile cells are converted to free-floating motile cells [60, 61]. Finally, they can either form a new biofilm in a new area or they can get attached to the same region and recolonize [62].

Molecular mechanism

The decision of bacteria to either live as a planktonic form or to produce matrix and form biofilm is regulated by c-di-GMP signalling [63, 64]. The lower cellular level of c-di-GMP results in down regulation of matrix constituent production, which leads to the detachment of bacteria from the surface. Higher levels of c-di-GMP promotes matrix component production and induces biofilm formation [65, 66]. In some Gram-positive bacteria and in all Gram-negative bacteria, the major regulator of biofilm formation is c-di-GMP [64]. The bacteria produces certain enzymes such as DGCs (Diguanylate cyclase enzymes) and specific PDEs (Phosphodiesterase enzymes) which regulates the specificity of this signalling process with its physical interactions with c-di-GMP effectors. In bacteria, DGCs contributes to c-di-GMP formation while PDEs aids the degradation of c-di-GMP [67]. In accordance to the environmental conditions, bacteria can live in any of the two forms (sessile or planktonic) by regulation mediated through the enzyme's regulatory domains in addition to its catalytic domains [68]. Both these enzymes, DGCs and PDEs have Gly-Gly-Asp-Glu-Phe (GGDEF) and Glu-Ala-Leu (EAL) / His-Asp-Gly-Tyr-Pro (HD-GYP) catalytic domains, respectively, which remains conserved [64]. Quorum sensing systems of Gram-negative bacteria use AHL (Acyl homoserine lactone) signal molecules produced by one or more AHL synthases. These signalling molecules can travel through the bacterial membranes and when they reach a threshold level of concentration, trigger one or more transcriptional factors and induce transcription of selective target genes. The correlation of signal molecule concentration to the bacterial population density enables the control of gene expression in a density-dependent manner [68, 69]. Quinolones are also employed as signalling molecules in both Gram-positive and Gram-negative bacteria. LuxI and LuxR homologue genes synthesizes HSL (Homoserine lactones), an auto-inducer which is also produced by Gram-negative bacteria. A transcriptional activator that senses the HSL is

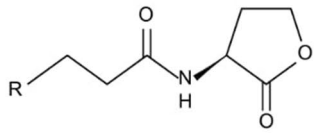
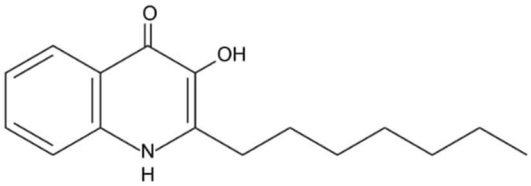
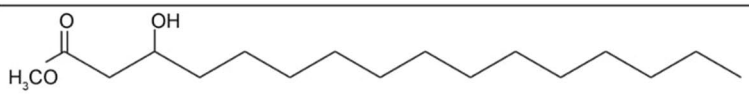
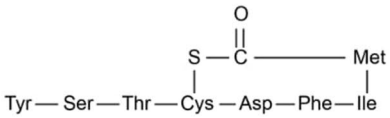
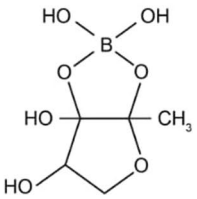
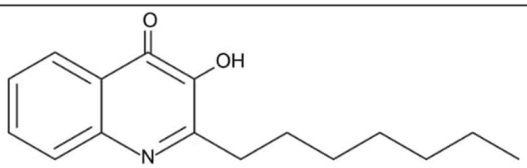
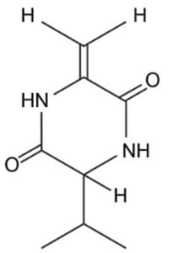
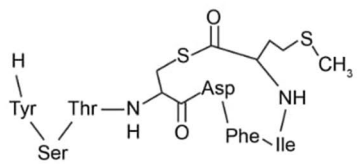
AHL	
PQS	
PAME	
Autoinducing Peptide (AIP)-I	
AI-2 (S-THMF-borate)	
hydroxyquinolones	
cyclic dipeptides	
oligopeptides	

Fig. 4 Quorum sensing modulators

encoded by these homologous genes [70]. Some of the quorum sensing modulators are represented in Fig. 4.

Clinical aspects

Although there have been advancements in the clinical field, biofilm infections caused by bacteria are still considered to be a major threat to human health. Lam, Hoiby and his teammates initially pointed out the fact that the recurrent infections are correlated with the biofilm formation, principally by *Pseudomonas aeruginosa* in cystic fibrosis patients [71, 72]. As time passed, the major source or cause for the tissue associated infections are accepted to be biofilms [73]. Even though there is a possibility of biofilm infections in humans due to hospital environment or previous existence, most of these tissue related biofilm illness have been developed in patients as a consequence of impaired immune system and chronic ailments like cancer, diabetes, cardiovascular disease, breakage of skin barrier [74]. The medical devices, most commonly pacemakers, peripheral vascular catheter that are used in the human body provides a surface for the bacteria to attach and form biofilms which eventually leads to infections; more over urinary infections, central line bloodstream infections, pacemaker infections, ventilator pneumonia are the other common device associated infections caused by biofilms [75, 76].

Even though the microbial antigens trigger the antibody production, there is no effective killing of bacteria present in the biofilm; the immune response by the antibody may also damage the tissues in its vicinity [77]. Antibiotic treatment do not affect the biofilm; it only affects the planktonic cells released from the biofilms [75]. Removal of the biofilm from the living tissue and the removal of the biofilm affected implants are the main ways to eradicate or avoid periodic infections [78]. Biofilms are responsible for various clinical infections such as dental caries, otitis media, periodontitis and osteomyelitis [60] and pulmonary infections seen in cystic fibrosis patients. Biofilms also causes health care associated infections, majorly including bacteremia, lower respiratory tract, surgical site and urinary tract infections which are developed due to pathogens that are opportunistic that mainly occur when a medical device has been inserted [10]. Catheters are much needed for the administration of drugs, blood products, nutrition and fluids into the veins; to filter the waste and water from the blood by haemodialysis; and to track the flow of blood within the organs and tissues of the body. The use of catheters paves way to a major health concern as it allows the growth of microbes on their surfaces, which eventually leads to infections causing serious health-related problems collectively named as CRBSIs (Catheter-related bloodstream infections). These infections were roughly calculated to amount to a total of 250,000 occurrences each year in the USA that are ruinous, involving a significant rate of disease and death in a population, in addition to an increase in health maintenance costs [79, 80].

The bacteria and microbes colonizing inside the catheter has the ability to avoid the host's immune system and also the effect of antibiotics. Finally, the bacteria enters the blood stream by separating themselves from the biofilm, thus leading to metastatic infections and CRBSIs. Several measures are taken to reduce the rate of CRBSIs; among them, a major preventive measure is the development of locked catheter lumens using solutions with antimicrobial properties and using antimicrobial agent-coated catheter surfaces [10]. Biofilms also have its existence on tumour cells say in colorectal cancer. They may also be considered as the secondary cause for the tumour formation, since the initiation of tumour itself is due to the impairment of the mucus barrier [81] that may provide the conditions for the formation of biofilm. The tissue structure in the confined region is damaged because of the local immune response that occurs due to the presence of tumours. So the bacteria can effortlessly acquire its niche. Mucus production in tumour cells increases when there is a coordinated action between the bacterial biofilm and inflammation. Thus, the mucus released by these cells serves as a constituent for the formation of potent biofilms [82].

Bacterial biofilm infections involve both device-associated and non-device-associated infections. For example, pacemakers, mechanical heart valves, urinary catheters, peritoneal dialysis catheters, voice prostheses, central venous catheters, prosthetic joints and contact lenses are the examples of major medical devices placed inside the body that formed biofilms on the surface or inside the device [83]. There are two types of contact lenses: soft and hard, on which microbes can attach. *Staphylococcus aureus*, *S. epidermidis*, *E. coli*, *P. aeruginosa*, species of *Serratia*, *Candida* and *Proteus*, etc., are the microorganisms that adhere to the contact lenses. According to the nature of the substrate, water content, bacterial type, electrolyte concentration and polymer composition, the strength of adherence varies. The most frequent reason for lens contamination is biofilm formation in the contact lens store cases [84]. In consonance with the nature of the fluid delivered by means of a central venous catheter, the multiplication of microbes may be influenced; for instance, the effect varies in both types of bacteria; growth in the fluids are sustainable in some Gram-negative aquatic species like *P. aeruginosa*, *Klebsiella* species and *Enterobacter* species, whereas in some cases microbes do not show proper growth in intravenous fluids; these include Gram positive bacteria, like *S. aureus* and *S. epidermidis* [85, 86].

Bacteria such as *S. epidermidis*, *S. aureus*, *Streptococcus* species, Gram-negative *Bacillus*, *Candida* and *Enterococcus* species are attached to the mechanical heart valves and the tissues present in the surroundings and develops biofilm on them. This uncomfortable state is known as prosthetic valve endocarditis [87]. *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *E. coli*, *S. epidermidis*, *E. faecalis*, *Proteus mirabilis* and other Gram-negative bacteria generally establish biofilms on urinary catheters [88]. This severely affects the health of the public and also affects instrumental and surgical procedures. Non-device-associated diseases produced by biofilms comprise persistent respiratory infections found in patients with cystic fibrosis, tuberculosis, chronic obstructive pulmonary diseases, chronic sinusitis, chronic wound infections, endocarditis, dental caries, chronic otitis media, biliary tract infections, osteomyelitis, bacterial prostatitis and periodontitis. Bacteria within the biofilm gained antibiotic resistance when there is only minimal regular exposure of antibiotics to the soft tissues inside the lungs or intestine. This minimal exposure may also affect the phenotypic and genetic variability in biofilm, bacterial physiology and also the potential of antibiotics to act as signalling molecules [89].

Non-device-associated infections also cause health issues. These infections occur in the oral gums, damage the bone where the teeth are held and in addition, affect the soft tissues. Poor oral hygiene causes such damage and tooth loss may also occur [90]. This infection is known as periodontitis in which the causative organisms are *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, which can form biofilms in the oral cavity on the mucosal surfaces [91]. The entry of the bacteria into the bloodstream sometimes helps the bacteria enter the bones and infect the metaphysis of the bone, leading to osteomyelitis. Then WBCs are recruited to the site and they secrete enzymes to lyse the pathogens and to phagocytose them. Sometimes, these lysing enzymes may cause damage or lysis to the bone, forming pus and circulate it through the bone blood vessels. This causes a block in the normal blood flow, leading to the damage of tissues and loss of function in the affected area [92, 93].

One of the most important biofilms in the human body is dental plaque. On the surface of the teeth, diverse microbial communities build up. These plaques are contained in a polymeric matrix that is bacterial and salivary in origin [94]. The dental biofilms are primarily constituted by organic and inorganic materials on which micro-organisms exist. Dental plaques contain about 20% carbohydrates by dry weight, of which 2–10% constitutes homopolymers of glucose (glucans). The enzyme glucosyltransferases, extracellularly converts sucrose into glucans [95, 96]. Fructans (fructose polymers) are produced by fructosyltransferases from sucrose [97]. At the initial stage of plaque formation, *Neisseria* and Streptococci were the pioneer species. Most predominant among them were *S. sanguis*, *S. oralis* and *S. mitis* [94]. After the plaque was transformed into a mature community, the fraction of pioneer species steadily reduced while that of anaerobic bacteria including *Fusobacterium*, *Veillonella*, and *Actinomyces* grew. These anaerobic bacteria are established in the deeper layers of the plaque [98].

The bacteria inside the biofilms are in close proximity; therefore, the metabolic product (lactate) of the primary feeder (Streptococci) is utilized as a source of nutrition by the secondary feeder (*Veillonella*). This interaction can exert a controlling influence on the enamel demineralization by strong bacterial acids. Since lactate is converted to weak acids like acetic and propionic acids by *Veillonella* spp., caries causing ability of other plaque bacteria are reduced. Some oral bacteria produce inhibitory factors that are antagonistic in nature, among them bacteriocins are the most common antagonistic compound. Bacteriocins are bacterially derived antimicrobial peptides with high molecular weight. Examples of bacteriocins produced by oral streptococci are sanguicin produced by *S. sanguis* and mutacin by *S. mutans*. They are also produced by *A. actinomycetemcomitans*, black-pigmented anaerobes and *C. matruchotii*. Despite the fact that bacteriocins typically have a narrow range of action, several of the streptococcal bacteriocins have a broad spectrum of activity and can inhibit organisms from a variety of gram-positive genera, including *Actinomyces* spp. Similar to this, a bacteriocin from *S. sanguis* proved effective against both Gram-positive and Gram-negative bacteria, including species of *Capnocytophaga* and *Prevotella*. [94].

There is also another category of biofilm disease which is biofilm-related device malfunctioning. When a medical device is implanted, there is inflammatory and wound healing responses in the body since the device incorporated is a foreign body. There are several steps in a foreign body reaction [99] in which the surface properties of the biomaterial play a significant role in modulating these reactions. These modulations happen for two to four weeks once the medical device is implanted; but the foreign body reactions persists in the tissues and biomaterial contact regions until the implanted device is present inside the body [100]. The failure or malfunction of the clinical implant paves way to the appearance of mild symptoms like slight contracture or functional disability of soft tissue along with negative inflammatory markers and light pain [101, 102]. The malfunction of the biofilm associated medical device brings about disastrous clinical issues that includes physical damage and chemical degradation of the pacemaker leads, biliary tube blockage,

malfunction of cerebrospinal fluid shunt, breast implant capsular contracture, crystalline encrustations on urinary stents, prosthetic joint failure and intravascular catheter malfunction. Finally, all these conditions lead to increase in morbidity and mortality, removal of implants and added hospital charges. Colonization of *C. tropicalis* and *C. albicans* on the transdermal endoscopic gastronomy feeding tubes give rise to polyurethane degeneration [103].

Inhibition of biofilm

Plant extract possess antibiofilm activity against biofilms produced by different microorganisms. The rhizome extract of *Hedychium larsenii* contained a compound Linalool in its essential oil that exhibited potential antibiofilm activity against *Streptococcus pyogenes* [104]. Eugenol obtained from the essential oil of *Syzygium aromaticum* (L.) Merr. & L. M. Perry (clove) leaf, suppressed the biofilm formation of an oral anaerobe *Porphyromonas gingivalis* [105]. The essential oil extracted from the leaves and flowers of *Plumeria alba* displayed good potential to inhibit the formation of *Pseudomonas aeruginosa* biofilms [106]. Most of the biofilm inhibitors are isolated from natural sources; some synthetic compounds, enzymes and chelating agents also possess anti-biofilm activity. Usnic acid, a secondary metabolite produced from lichen; synthetic halogenated furanones, bacteriophage-encoded endolysin (PlyC) and enzymes like Deoxyribonuclease I, glycoside hydrolase (dispersin B) are examples of other biofilm inhibitors [107–110]. Certain promising methods are developed from the existing hindrance mechanism that prevented biofilm formation, other than the common antibiotic therapy [111]. The two main novel strategies against the biofilm are the blockage of quorum sensing and enzyme-mediated biofilm inhibition.

By blockage of Quorum sensing

Quorum sensing (QS) has been considered as a significant mechanism in the synthesis of biofilms; hence, its blockage is one of the major strategies to inhibit the biofilm. The QS inhibitors prevent the communication among the bacteria, and this makes the bacteria sensitive to the antibiotic response and host immune system [112, 113]. Therefore, in order to control biofilm-associated infections, QS is considered as an effective target. Quorum quenching is the repression of QS sensing; in this mechanism, the communication signals are blocked by structural modification or by competitive inhibition, instead of degrading them [114, 115]. The antagonist of QS bound with signal molecules or with the receptor on which the signal molecules are usually bound; in either way, the receptor-signal molecule interaction has been disabled [116]. There are three main strategies used to block quorum sensing in Gram-negative bacteria: AHL biosynthesis blockage, AHL degradation or inactivation and signal receptor interference [117]. Various reactions take place sequentially during the AHL biosynthesis. To produce the homoserine lactone ring in the AHL, SAM (S-adenosyl methionine) is utilized. The acyl side chain in AHL is produced from an acyl carrier protein (ACP) precursor molecule that is charged sufficiently [118–120]. According to Zano et al. [121] and Masevicius and colleagues [122], for methylation processes, S-adenosyl-L-methionine (AdoMet) is produced by various Gram-negative bacteria as an initial methyl donor [117]. Two types of signal molecules involved in QS are synthesized from AdoMet and hence inhibition of AdoMet can cause the prevention of biofilm formation as reported by Zano et al. [121] [117]. S-adenosylhomocysteine and S-adenosylcysteine, analogous to SAM, are effective inhibitors that hindered the biosynthesis of AHL [118]. The AHL molecule biosynthesis of *P. aeruginosa* is shown to be inhibited by antibiotics like erythromycin and azithromycin when delivered at sub inhibitory concentrations. This suppression restricts the virulence factor and inhibits the biofilm formation [123–125].

AHL degradation or inactivation is a promising tactic to eliminate bacterial infections associated with biofilms. By enzyme activity, the AHL molecules are also degraded, thus avoiding the accumulation of AHL. The homoserine lactone ring of AHL is exposed without any disturbances to the rest of the molecule, by breaking the leftward bond of the double bonded oxygen with AHL lactonases and the bond present on the rightward of the double bonded oxygen is broken by enzyme decarboxylases. AiiA 240B1 produced by *Bacillus* spp. 24B1 is the first protein molecule identified to have the capability to hydrolyze the lactone ring of AHL molecule [126]. In the AHL molecule, the AHL acylase hydrolyzes the amide bond that is between the acyl side chain and homoserine lactone. This hydrolysis reaction in turn releases free fatty acid and homoserine lactone [127]. The carbon atoms in the acyl chain of this signal molecule are oxidized by utilizing AHL oxidase [128]. AHL signal molecules has not been broken by AHL oxidoreductases but has undergone alteration by which the binding efficiency of the signal molecule with the receptor proteins was modified [129].

Another strategy to prevent quorum sensing is the interruption of receptor molecules by analogous compounds. The physiological behaviours, mainly biofilm activity, virulence and antibacterial tolerance, are reduced in a bacterial community when the signal recognition is not happening. This is achieved when there is an interference in the binding of the AHL signal molecule with the receptor protein. The interruption is caused due

to the binding of antagonist molecules with the receptors, making the receptor unavailable to the signal molecule for binding. In *Staphylococcus epidermidis*, an efficient QS inhibitor, furanone has been identified as an analogue molecule that successfully inhibits biofilm formation [130]. In some cases, the antimicrobial peptides also affect biofilm formation, besides the three strategies mentioned above. These peptides could hinder the QS system by either disturbing the transport of the signal molecules outside or within the cell, through which the cascade of signal transduction and the formation of biofilms are affected. CRISPRi is a recent technology applied in the latest research to minimize biofilm formation in *Escherichia coli* by blocking lux gene expression at the time of QS signalling [131]. Targeting c-di-GMP signalling systems is also considered as an efficient strategy to control biofilm [132].

By enzyme activity

Certain enzymes act as antibiofilm agents to remove the biofilm that had already formed. These include six main categories, such as oxidoreductases, transferases, synthetases, ligases, lyases and hydrolases. The cells from the bacterial biofilm are released from it when its disintegration happens due to the activity of saccharolytic enzymes yielded by some bacteria [133]. The enzymes block adhesive production and EPS formation, thereby inhibiting biofilm formation [134]. In biofilm formation, starch is a vital chemical component [135]; therefore, biofilm removal results due to polysaccharide degradation [133]. Biofilms of various bacteria are disrupted by some enzymes like protease, glycosidases and DNase, which are produced by the bacteria itself. These enzymes degrade the matrix, and therefore, the biofilms are dispersed. DNase has an inhibitory action on biofilms formed by both types of bacteria [136].

At the initial stage of biofilm formation for the existence of biofilm in a long run and to provide intactness, the extracellular DNA (e-DNA) play a significant role in the attachment of bacteria, matrix accumulation, stability, regulation and biofilm formation [137, 138]. According to Nijland and co-workers [139], the e-DNA in the EPS matrix of biofilm is dispersed by using DNase (NucB) [117]. In *Staphylococcus* species, biofilms have been reported to be inhibited by various proteases like trypsin, proteinase K, chymotrypsin, carboxypeptidase A and serratiopeptidase [140]. Alginate lyase produced from the marine bacterium source is considered an enzyme involved in biofilm disassembly [141–144]. *Pseudoalteromonas* is a marine bacterium from which the alginate lyase has been retrieved and it displays inhibitory action against biofilms formed by *S. enterica*, *P. aeruginosa* and *E. coli* [145, 146].

A potential antibiofilm activity has been found in amylase [147]. Alpha amylase aids the inactivation and eradication of the biofilm formation in *S. aureus*, as reported by Craigen and co-workers [148]. α amylase is considered as the most potent enzyme in polysaccharide inhibition from the investigation conducted by Divakaran et al. [149]. A combination of different enzymes is employed for biofilm eradication rather than using a single enzyme. The combined action of amylase, dextrin hydrolase and levan hydrolase has helped in biofilm removal [150]. Three enzymes like alpha-amylase, beta-glucanase and protease combined is found to be advantageous in industrial slime removal [151]. Various plant extracts are also reported to be effective against biofilm by having antivirulence, antiseptic and anti-QS properties and can damage the structure of mature biofilm and also prevent biofilm formation. Fresh *Allium sativum* extract displays competent activity against biofilms [152]. The different stages of biofilm formation and their inhibitors at each stage are represented in Fig. 5.

Proposed mechanism

The enzymes like amylase break down the exopolysaccharide of bacteria that are attached to the surface as biofilms. The starch in the exopolysaccharide is broken down into sugars. Due to this, the bacteria in the biofilm are detached, and thus, further biofilm formation is inhibited. The exo-amylases and endo-amylases are the two groups formed by the classification of amylases on basis of the mode of action. End products formed are shorter when the substrates are hydrolyzed by exo-amylases and these enzymes act from the substrate's non-reducing end [154], while oligosaccharides (end products) of different lengths are produced when the endo-amylases act unevenly on the glycosidic linkage present internal to the starch molecule [155]. Starch is a polysaccharide with amylose and amylopectin glucose polymers that are considered the main substrate on which α-1,4-glucan-4-glucanohydrolase efficiently acts. A disaccharide (maltose) and a monosaccharide (glucose) are produced when the α-1,4 and α-1,6-glycosidic bonds are hydrolysed with the help of α-amylase [133]. This enzyme needs Ca^{2+} metals for its stability since it is a metalloenzyme [156]. α-amylase can proceed with its action on the substrate from anywhere and can act faster, whereas β-amylase acts on α-1,4-glycosidic bond exclusively from the non-reducing end of starch. This is the cause for the higher inhibitory action of α-amylase compared to β-amylase [157]. Figure 6 depicts the proposed mechanism of biofilm inhibition.

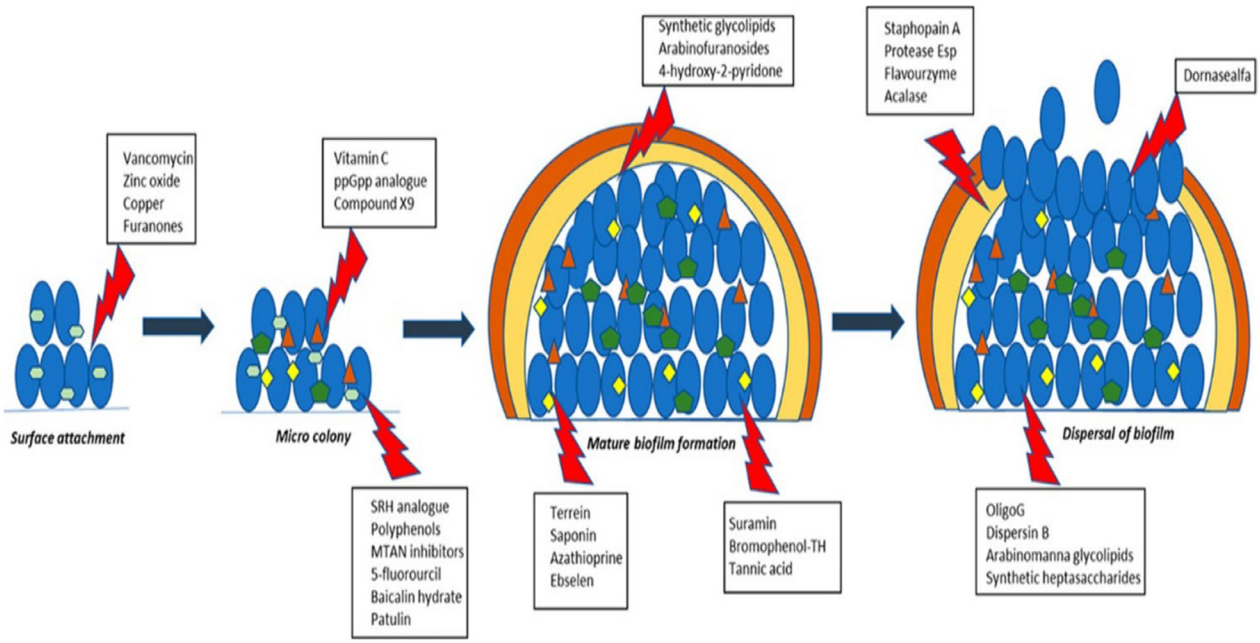


Fig. 5 Different stages of biofilm formation and their inhibitors. Ghosh A et al. [153]. ©https://pubs.acs.org/doi/10.1021/acsomega.9b03695

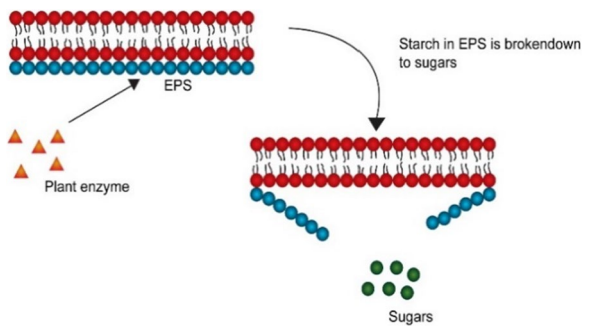


Fig. 6 Proposed mechanism of biofilm inhibition

Conclusions

Biofilm formation is an advantageous strategy employed by bacteria to protect themselves from antibiotics and to ensure their survival in stressful environmental conditions. Cell-to-cell and cell-to-surface adherences are assisted by the bacterial polysaccharide. The communication between the cells is regulated by quorum sensing, which utilizes auto-inducers as signalling molecules. The biofilms are pathogenic and cause several device and non-device-related clinical problems. To get rid of biofilms, either quorum sensing or c-di-GMP signalling is targeted. There are different enzymes which hinder the formation of extracellular polymeric substances and also disintegrate the matrix, which leads to the disassembly of biofilm. Plant extracts can also promote biofilm eradication since some of them have anti-QS compounds.

Abbreviations

EPS	Extracellular polymeric substances
TA	Teichoic acid
LPS	Lipopolysaccharides
AIP	Autoinducing peptides
AHL	Acyl-homoserine lactones
AI-2	Autoinducers-2
CWA	Cell wall-anchored
MSCRAMMs	Microbial surface components recognizing adhesive matrix molecules
eDNA	Extracellular DNA
QS	Quorum sensing
DGCs	Diguanylate cyclase enzyme
PDEs	Phosphodiesterase enzymes
GGDEF	Gly-Gly-Asp-Glu-Phe
EAL	Glu-Ala-Leu
HD-GYP	His-Asp-Gly-Tyr-Pro
HSL	Homoserine lactones
CRBSIs	Catheter-related bloodstream infections
SAM	S-adenosyl methionine
ACP	Acyl carrier protein
AdoMet	S-adenosyl-L-methionine

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Author contributions

Dr. KV conceived the idea and outlined the content; Ms.SV collected information, reviewed the literature and developed the manuscript; Dr. KV and Dr. BM proofread and edited the manuscript. All authors read and approved the final manuscript for submission.

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Availability of data and materials
The datasets used for the current study were collected from the journals, by using Google Scholar, Science Direct, PubMed, Springer link, JSTOR, etc. Conference papers, books were also used in this study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Informed consent for publication of image within the text [Ghosh A, Jayaraman N, Chatterji D (2020) Small-Molecule Inhibition of Bacterial Biofilm. ACS Omega 5(7):3108–3115. Direct link: < https://pubs.acs.org/doi/10.1021/acsomega.9b03695 >] was obtained to be published in the above journal and article. Further permission related to the material excerpted should be directed to the ACS.

Competing interests
The authors declare that they have no competing interests.

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