Role of Biosurfactants in Biofilm Prevention and Disruption

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1 Introduction

1.1 Biosurfactant

Biosurfactants are surface-active agents produced by several species of bacteria and yeast. The molecules could be high molecular or low molecular weight cell-bound or cell-free secondary metabolites. Structurally composed of hydrophobic and hydrophilic moieties, biosurfactants are amphiphilic molecules. This structure of biosurfactant facilitates the efficacy of biosurfactant in decreasing the surface tension of various mediums as well as air-water interfacial tension. Owing to their unique structure, biosurfactants are reported to have immense application potential in various sectors such as agriculture, pharmaceutical, cosmetics, food sectors, bioremediation, etc. (Nguyen et al. 2008; Akubude and Mba 2021; Aslam et al. 2021).

The low molecular biosurfactants are classified as glycolipid, lipopeptide, fatty acids, and polymeric surfactants based on the structure. Glycolipids are the biosurfactant that has a carbohydrate moiety attached to a hydrophobic fatty acyl chain consisting of 8–18 carbon. The fatty acyl chain is a long hydroxyl fatty acids chain connected with either an ester or ether group. Based on the carbohydrate

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moieties, glycolipids are classified as rhamnolipid, sophorolipid, mannosylerythritol lipid, and trehalose lipid (Malakar and Deka 2021). Glycolipids are produced by a diverse array of bacteria, and fungi and have tremendous multifarious activities. The lipopeptides consist of peptides attached to a fatty acyl chain. The lipopeptides are classified as surfactin, iturin, and fengycin. Various high molecular weight biosurfactants such as corynomycolic acid, spiculisporic acid, agaricic acid, emulsan, liposan, alasan, and lipomanan are also reported to be produced by several microbial communities (Fujii et al. 1999; Mulligan and Gibbs 2004; Santos et al. 2016; Vijayakumar and Saravanan 2015) (Fig. 1).

These classes of secondary metabolites are produced in response to several environmental conditions by a large number of microbes. Bacteria and yeast belonging to genera of *Pseudomonas*, *Bacillus*, *Rhodococcus*, and *Candida* are reported to produce different types of biosurfactants (Singh et al. 2019). Various species of *Pseudomonas* are reported to produce rhamnolipid, a type of glycolipid structurally composed of one or two rhamnolipids attached to a fatty acyl chain. Species of *Burkholderia* such as *Burkholderia glumae*, *Burkholderia thailandensis*, and *Burkholderia plantarii* are also reported to produce rhamnolipid (Costa et al. 2011; Dubeau et al. 2009; Hörmann et al. 2010). Another form of glycolipid, Sophorolipid is structurally composed of sophorose attached to the lipid chain. They are mainly produced by non-pathogenic yeast such as *Starmerella bombicola*, *Candida batistae*, *Rhodotorula babjevae*, etc. (Costa et al. 2018; Kim et al. 2021; Sen et al. 2017). Sophorolipid has recently been intensely studied owing to multifarious activities. The lipopeptide viz. surfactin, iturin, and fengycin are produced by various *Bacillus* species. Various lipopeptides producing bacteria produce one, two, or all three types of lipopeptides. The lipopeptides are well-known for their antimicrobial activities against a wide range of the pathogen. Surfactin is reported to exhibit more antibacterial activity while fengycin produces effective antifungal activity.

In recent decades, biosurfactants have received enormous interest owing to their multifarious activities. The antimicrobial activities of almost all the discovered biosurfactants have been reported. The presence of a hydrophilic head and hydrophobic tail gives the biosurfactant a structural resemblance with the lipid bilayer of the cell membrane. As a result, biosurfactant exhibits antimicrobial activity by inserting the lipid chain into the lipid bilayer. This results in the cell membrane disintegration and changes in cell membrane permeability. Consequently, the intercellular materials leakage results in cell death (Yalcin and Ergene 2009; Vatsa et al. 2010; Otzen 2017; Sana et al. 2018). Several studies revealed the antimicrobial activity of biosurfactants indicating its efficacy in pharmaceutical fields. An antimicrobial agent needs to exert antibiofilm activity on the pathogen to prevent the recurrence of infection. In this regard, biosurfactants can be a potential alternative as several works of literature report the antibiofilm activity of various types of biosurfactant.

Work involving the antibiofilm strategy of biosurfactants is still in laboratory conditions. The practical antibiofilm application of biosurfactant has not yet developed into a commercial prospect. In the last 5 years, several work has been published

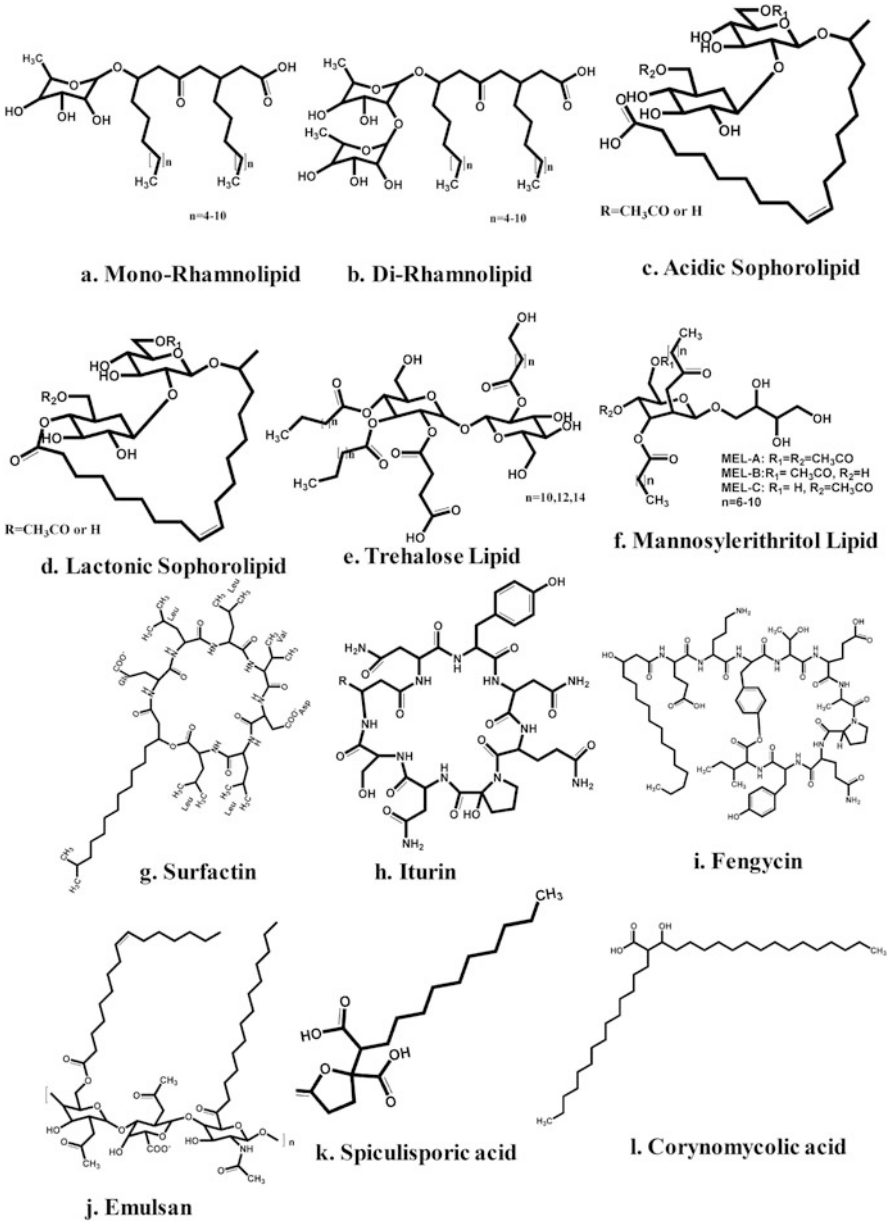

Fig. 1 Structural representation of various types of biosurfactants

which highlights the efficiency of biosurfactant in exhibiting antibiofilm activity. Various types of biosurfactant are investigated, where they have shown efficient antiadhesive, biofilm inhibition and biofilm disruption activity. Figure 2 indicates the increasing amount of work in the biofilm in several sectors.

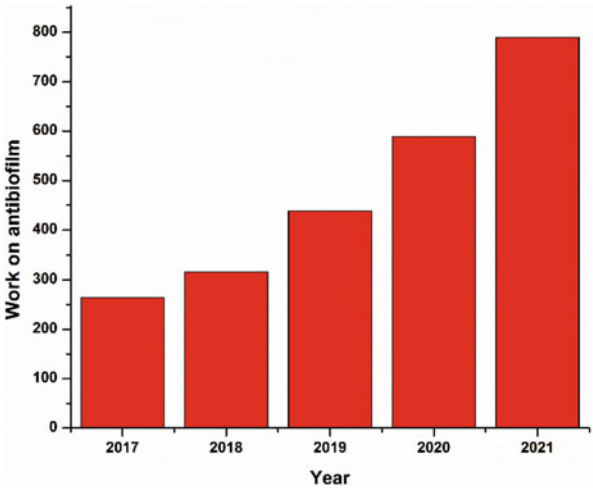

Fig. 2 Work done on antibiofilm activities of biosurfactant in the last few years

2 Biofilms

The world of microorganisms is very complex. The microbial flora has several impacts on various life forms on the earth. They are an integral part of the food, indigenous flora of several host bodies, and are often part of the gut microflora. The microbes are known to render various beneficial as well as harmful impacts on the host. Although the microbes survive as an individual colony-forming unit, in several cases, they tend to aggregate to form the biofilm. Thus biofilms are an important adaptation and survival strategy commonly employed by bacteria, yeast, and fungal pathogen. Biofilm could be composed of a single type of organism or different microbial colonies, adhered to a given substrate. The biofilm is composed of single or multiple species of the microbes attached while being embedded in an extracellular polymeric substance, known as the exopolysaccharide (EPS). This exopolysaccharide is composed of eDNA, proteins, and polysaccharides (Sharma et al. 2019). Biofilm-associated cells regulate specific genes that have impacts on growth rate. In a complex biofilm, consisting of several species of microbes, the close proximity of the microbes in a biofilm enables the microbes to exchange substrate, various metabolic products, and removal of toxic end products (Hollmann et al. 2022). The formation of biofilm is a multistep approach involving (a) surface adsorption of macro and micro molecules; (b) microbial adhesion to the substratum, (c) EPS production; (d) colony aggregation, and (e) biofilm maturation (Fig. 3).

Biofilm formation is initiated by attachment of microbes to the substratum which is regulated by diverse factors such as growth condition, substratum, and cell surface properties. The type of substratum determines the growth of the biofilm on it. In order to form the biofilm, the planktonic cells must adhere to the substratum. The growth of biofilm is believed to be better on rough and hydrophobic substrates. In addition to this, biofilm formation is also dependent on the type of the microbial

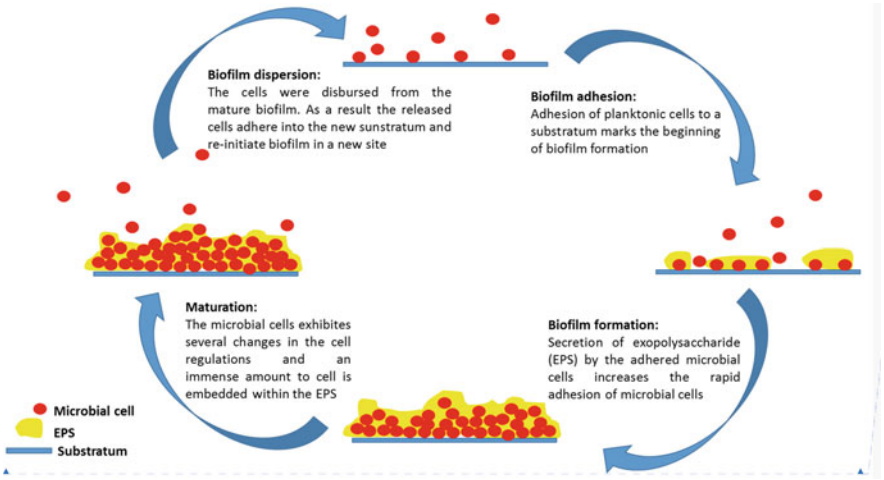

Fig. 3 Steps of biofilm formation

cells. Cells with flagella, pili, fimbriae, or glycocalyx are reported to exhibit efficient attachment of the microbes to the substratum. The cell surface hydrophobicity of the microbial cells is reported to play an important role in microbial attachment to the substratum (Donlan 2001). In certain cases, several microbial colonies form a mobile biofilm that is devoid of the attachment of microbes to the substratum. Cells are thus irreversibly attached to the substratum, which then undergoes cell division to produce micro- and macro-colonies of the microbes.

The attachment phase is followed by the initiation of biofilm formation. Once the cells were successfully attached to the substratum, the microbial cells start to form a monolayer of the microbial cells and secrete exopolysaccharide (EPS) consisting of extracellular polysaccharides, structural proteins, cell debris, and nucleic acids. Initially, the EPS consists of extracellular DNA (*eDNA*) which is ultimately taken over by polysaccharides and structural proteins. Simultaneously there is the formation of microcolonies which exhibits significant growth and quorum sensing. EPS are highly hydrated (98% water) and have micro "water channels" to allow the cells growing within the biofilm to have an access to essential nutrients and oxygen. Biofilm-associated organisms grow more slowly than planktonic organisms.

The microcolonies then start growing on the substratum and eventually develop into a mature biofilm. The biofilm develops in three dimensions. The biofilm architecture of various microorganisms is mediated by EPS molecules, which produces a spatial organization to facilitate cells cluster in microcolonies. The final biofilm formed is a multilayered microbial community. A mature biofilm consists of 10^8–10^{11} cells per gram wet weight, which might comprise of the same or several different species (Flemming et al. 2016).

Biofilms are reported to be omnipresent, thus rendering several harmful as well as beneficial effects. Microbial biofilms are reported to be present in tooth enamel surfaces in the oral cavity, ship hulls, medical devices and thus are responsible for

chronic illness, nosocomial infections, industrial pipe fouling, spoilage and contamination of foods, as well as ship hull fouling (Muhammad et al. 2020).

2.1 The Adaptive Beneficial Impact of Biofilm on Microbes

Biofilm renders several adaptive advantages to the microbial colonies involved in the biofilm. Microbes bound to a biofilm tend to resist nutrient deprivation, changes in pH, oxygen radicals, disinfectants, and antibiotics better than planktonic organisms (Jefferson 2004). The biofilm provides a local lifestyle for the microbes affected by stage-specific expression of genes and proteins. The biofilm exopolysaccharide acts as an interface between the biofilm and its environment, enabling its interaction with the surrounding environment. The essential component of the biofilm is the exopolysaccharide which contains water-soluble and water-insoluble components of the matrix. The water-soluble components are gel-forming polysaccharides, proteins, and eDNA, and water-insoluble components are amyloids, cellulose, fimbriae, pili, flagella, etc. (Flemming et al. 2016; Ibanez de Aldecoa et al. 2017). Among these components, eDNA is reported to play an important role in the formation of biofilm and the production of extracellular matrix, which stabilizes the biofilm structure. The eDNA could also be the source of horizontal gene transfer, providing several adaptive capabilities to the microbes within the biofilm. Recent studies have revealed that biofilm is a thousand times better in retreating the effect of antibiotics. Antibiotic resistance has been an emerging global concern as this has failed the effectiveness of several types of antibiotics. Microbes in the biofilm receive protection against antimicrobial drugs, environmental stresses, the host immune system, and shear forces (Santos et al. 2018). In many cases, the biofilm acts as a mediator for horizontal gene transfer, which can sometimes cause the acquisition of antibiotic-resistant genes among the microbes participating in the biofilm.

Biofilm is the microbial society wherein individual microorganisms as well as microbial communities communicate within the biofilm to initiate different physiological processes and cooperative activities. This behavior is influenced by small diffusible autoinducers that are produced by the microbial community within the biofilm (Berlanga and Guerrero 2016). Biofilm offers the opportunity for changes in the microbial cells owing to gene regulation, thereby inciting the formation of novel genetic changes (Fig. 4).

2.2 The Genetic Prospect of Biofilm Formation

Successful production of biofilm is regulated by the up- and downregulation of several genes. Upregulation of *algD*, *algU*, *rpoS*, and genes controlling polyphosphokinase (PPK) synthesis are reported to play a significant role in the biofilm formation of *P. aeruginosa* (Pulcini 2001). Various genes play an important

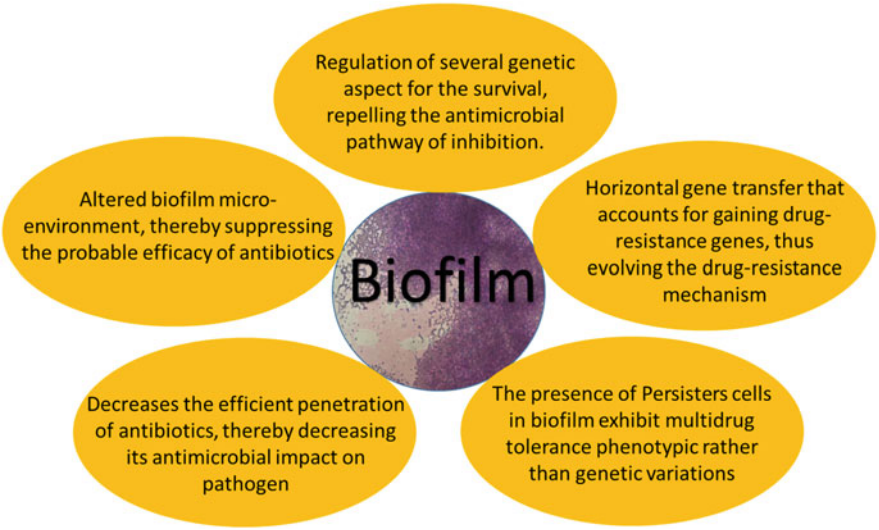

Fig. 4 Beneficial impact of biofilm formation on the microbial community

role in the synthesis of biofilm matrix such as *csgA*, involved in the synthesis and aggregation of colanic acid protein in *E.coli* (Jefferson 2004). *algC* gene, required for alginate synthesis in *Pseudomonas aeruginosa* plays an important role in maintaining the pathogen biofilms (Davies et al. 1993). In the case of gram-positive biofilms such as in the biofilm of *S. mutans*, sucrose-dependent polysaccharide production and biofilm formation are influenced by Glucan binding protein *GbpA* (Loo 2003). Intercellular adhesin locus (*icaADBC*) in *Staphylococcus aureus* and *Staphylococcus epidermidis* are reported to encode the genetic products responsible for the synthesis of a β-1-6-linked poly-*N*-acetylglucosamine polymer called PNAG or PIA (polysaccharide intercellular adhesin) (Heilmann 2003).

Biofilms of *Staphylococcus aureus* were reported to upregulate genes encoding enzymes involved in glycolysis or fermentation due to oxygen limitation in the developed biofilm (Becker et al. 2001). Owing to the upregulation of certain genes and downregulation of other genes, the metabolic activity of the biofilm embedded cells is altered compared to the planktonic cells. Nakamura et al. (2016) reported that in a biofilm, genes involved in the biosynthesis of other secondary metabolites, xenobiotics biodegradation and metabolism, lipid metabolism, membrane transport, amino acid and carbohydrate transport, biosynthesis of secondary metabolites, and stress response are upregulated, while the genes involved in the respiratory chain, nucleotide biosynthesis, fatty acid metabolism, and DNA repair are downregulated. Rumbo-Feal et al. (2013) reported the overexpression of 1621 genes in the biofilm of *A. baumannii* compared to stationary phase cells including 55 genes that were only expressed in biofilms, thereby causing changes in amino acid and fatty acid metabolism, motility, active transport, transcriptional metabolism, and quorum sensing. Thus, with several upregulation and downregulation of the genes, the organisms in

the biofilm community strive in the biofilm, being protected from several harsh environmental factors.

2.3 The Beneficial Impact of Biofilm

Several microbial biofilm and consortia are reported to exhibit various beneficial impacts in day-to-day anthropogenic activities. Rapid industrialization, urbanization, and exponential population growth have created major water contamination. In various cases, bacterial communities have been employed through biofilm-based wastewater treatment technology to neutralize and degrade organic and inorganic compounds in wastewater. (Muhammad et al. 2020). In this technology, biofilm-forming microorganisms are added to the wastewater which then utilizes organic and inorganic compounds present in the wastewater as nutrients. The pathogens present in the wastewater are also trapped by the biofilm, thereby cleaning the water (Sehar and Naz 2016).

Microbial biofilms are also part of various plant, animal, and human body systems. Along with rendering harmful effects, in certain cases, biofilm is reported to exhibit a beneficial impact. In the agriculture system, the biofilm of plant growth-promoting microbes renders efficient protection against several phytopathogens. Rhizobacteria colonize the roots of plants, thereby promoting plant growth through nitrogen fixation, mineral uptake, production of phytohormone, pathogen suppression as well as protection from both biotic and abiotic stresses (Goswami et al. 2020). Goswami and Deka (2020) reported that root colonization of *B. altitudinis* in mustard plants yielded better root architecture along with elevation of the growth factors. The root colonization of microbes mainly involves bacterial isolates belonging to the genera *Bacillus*, *Pseudomonas*, *Streptomyces*, *Serratia*, and *Stenotrophomonas* (Arrebola et al. 2019). Biofilm by *Paenibacillus polymyxa* in the rhizosphere of peanuts was reported to protect against crown root rot disease caused by *Aspergillus niger* (Haggag and Timmusk 2008).

Certain microorganisms can remediate hydrocarbon contaminated sites. The introduction of biofilm producing hydrocarbon-degrading microbes can remove the hydrocarbon from the contaminated sites (Upadhyayula and Gadhamshetty 2010; Rodríguez-Martínez et al. 2006). This formation of biofilm can enhance the rate of remediation of noxious hydrocarbon.

There are reports that certain bacterial strains can be used to prevent the corrosion of many metals. Zuo et al. (2004) reported that a cyclic decapeptide produced by biofilms of *Bacillus brevis* was effective in inhibiting corrosion-causing, sulfate-reducing bacteria (SRB), thereby preventing mild steel corrosion. Aerobic biofilms are reported to better prevent corrosion due to their efficient oxygen consumption (Kip and Van Veen 2015).

A huge number of beneficial microbes are present in the human gut. The gut microbiome plays a vital role in different metabolisms which were found to be present from the oral cavity to the large intestine (Hussain et al. 2020). This

colonization of gut microbes starts at birth or even before when the virtually sterile baby encounters new microbial environments (De Vos 2015). Biofilms formed by the gut microbiota use quorum sensing (QS) to coordinate their social behavior, thereby influencing host cell activities in a non-invasive manner (Deng et al. 2020). The colonization of various beneficial bacteria and yeast on several parts of the host body is reported to provide several benefits along with repelling pathogens (Byrd et al. 2018).

3 Biofilm: A Threat

Although, there are reports that biofilms have some beneficial impact, however, the harmful effect of it cannot be ignored. Biofilms are one of the major reasons for the recurrence of infection in many cases. Their presence is detrimental to several health aspects of the human and life stock. Biofilms have a detrimental effect on the food processing industry as biofilms may lead to food spoilage which would be harmful (Galie et al. 2018). Biofilm formed by *Listeria monocytogenes*, *Escherichia coli*, *Pseudomonas* spp., *Vibrio parahaemolyticus*, *Staphylococcus aureus*, *Geobacillus stearothermophilus*, and *Campylobacter jejuni* is reported to pose several health threats such as bacterial gastroenteritis, food spoilage, diarrhea, foodborne intoxications, and emetic syndrome (Muhammad et al. 2020). The persistence of various biofilms on drinking water distribution systems can be the cause of severe health hazards (Loveday et al. 2014). Biofilms of phytopathogen are reported to cause a detrimental impact on agriculture. Biofilm of pathogen tends to revert the effect of several antibiotics used in agriculture, thus impacting the agriculture yield. Pierce's disease of grapevines and citrus canker are reported to be caused by the biofilm produced by *Xanthomonas citri* and *Xylella fastidiosa* (Ference et al. 2018; Kyrkou et al. 2018). Biofilms produced by *Ralstonia solanacearum* is reported to be involved in the pathogenesis of tomato (Mori et al. 2016; Yao and Allen 2007). Biofilm produced by *Pseudomonas aeruginosa* on roots of *A. thaliana* and sweet basil is reported to kill the plants within 7 days (Danhorn and Fuqua 2007).

The most significant negative role played by the biofilm is its role in several hospital-acquired infections. The persistence of biofilms produced by pathogens in various medical devices such as breast implants, mechanical heart valves, joint prostheses, pacemakers catheters, ventricular shunts, contact lenses, prosthetic heart valves, cerebrospinal fluid shunts defibrillators, and ventricular-assisted devices are reported to exhibit several health threats (Darouiche 2004; Muhammad et al. 2020). Medical devices are often contaminated with biofilms produced by coagulase-negative *Staphylococci*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus* sp., *and Candida albicans* (Kokare et al. 2009). These contaminated devices might expose pathogens to the host internals, thereby resulting in fatal systemic infections. Recurrence of biofilm is reported to be a constant reason for the persistence of various infections. Among several pathogens, *S. aureus* and coagulase-negative *Staphylococci* are reported to

cause two-thirds of implantable device-associated Staphylococcal infections. Among several staphylococcal species, *S. aureus* and *S. epidermidis* are the leading cause of hospital-acquired, surgical site, and bloodstream infections with high hospitalized rates (Khatoon et al. 2018). Biofilm of pathogenic bacteria is reported to be the main cause of diseases such as cystic fibrosis (CF), chronic wounds, infective endocarditis (IE), periodontitis, otitis media, and osteomyelitis (Southey-Pillig et al. 2005; Akyıldız et al. 2013; Masters et al. 2019; Jamal et al. 2018). It is estimated that 65% of all bacterial infections and 80% of microbial infections are associated with biofilm (Jamal et al. 2018; Dhar and Han 2020).

The biofilm retreats the effect of several antibiotics, thereby failing their antimicrobial activity against the pathogens (Vestby et al. 2020). Different pathways are involved in the antimicrobial repelling activity of biofilms such as slow or incomplete penetration of the antibiotics into the biofilm, an altered chemical microenvironment within the biofilm, multicellular properties of the biofilm, EPS-mediated inhibition of the diffusion of the antibiotic into the biofilm. Antibiotic resistance of biofilm is rendered by the multicellular nature of biofilms (Sharma et al. 2019). Persisters cells are another type of cells in a biofilm in which the cells are in a dormant state exhibiting multidrug tolerance phenotypic rather than genetic variations (Helaine and Kugelberg 2014; Ayrapetyan et al. 2015).

3.1 Harm Rendered by Bacterial Biofilm

Bacterial biofilms are reported to be present in every inch of the earth. They colonize every living and non-living substratum, thereby becoming an inevitable part of several living and non-living systems. It is known that about 40–80% of bacteria on the planet form biofilm (Flemming and Wuertz 2019). Several superficial, internal, as well as systemic infections are reported to cause increased severity owing to the biofilm of the pathogen. Cystic fibrosis is a pulmonary infection caused by the persistence of *P.aeruginosa* biofilm (Southey-Pillig et al. 2005). Periodontitis is a biofilm-mediated infection that damages the gums, the soft tissues as well as bones supporting the teeth. The infection is reported to be caused by *Porphyromonas gingivalis*, *Actinobacillus*, *Prevotella*, and *Fusobacterium* (Listgarten 1986; Kanwar et al. 2017). *Enterococcus faecalis* and *Enterococcus faecium* are associated with nosocomial infections. These pathogens are well-known for causing biofilm-oriented infections which are often difficult to treat (Paganelli et al. 2012). Another condition such as Cholesteatoma is reported where the keratinizing squamous epithelium is trapped in the middle ear and/or in the mastoid process in which 81.3% of cholesteatomas are reported to be biofilm-associated (Galli et al. 2016; Kaya et al. 2013). Several chronic infections caused by bacteria are often reported to be biofilm-mediated (Wilkins et al. 2014). The biofilms produced by *Staphylococcus epidermidis* and *Staphylococcus aureus* are the causes of nosocomial infections and infections through medical devices frequently (Otto 2008). In a bacterial biofilm, around 1% of cells are antibiotic-resistant (Sharma et al. 2019). Approximately 95%

of urinary tract infections (UTIs) are associated with urinary stent and catheter tubes, while intravascular devices such as pacemakers, left ventricular assist devices, implantable cardioverter defibrillators, and prosthetic vascular grafts are reported to be associated with 87% of bloodstream infections, and 86% of pneumonia are associated with mechanical ventilation (Nandakumar et al. 2013). Twelve percent of hip periprosthetic infections are caused by *Propionibacterium acnes*, *Peptococcus saccharides*, *Peptococcus magnus*, and *Peptostreptococcus magnus* biofilm (Geipel 2009). 78.2% of the chronic wounds are reported to be associated with biofilm (Dhar and Han 2020).

3.2 Harm Rendered by Fungal Biofilm

The association of fungal biofilm has been reported to cause millions of infections yearly. Biofilms formed by *Candida* spp., *Aspergillus* spp., *Fusarium* spp., *Pneumocystis* spp., *Rhizopus* spp., *Rhizomucor* spp., *Cryptococcus neoformans*, *Blastoschizomyces capitatus*, *Malassezia pachydermatis*, and *Trichosporon asahii* have received the most attention due to their pathogenicity (Kernien et al. 2018). The persistence of fungal biofilm on various medical devices can cause fatal harm to patients with a high rate of morbidity. Patients with implanted medical devices or compromised immune systems may be highly susceptible severe, disseminated disease with high mortality caused by biofilms of *Candida* spp. (Douglas 2003). The fungal biofilm defers in the structure compared to bacterial biofilm. Various fungal biofilm is formed by the filamentous hyphae along with the exopolysaccharide. The biofilm formed by *Candida albicans* is reported to be progressed by hyphae formation, followed by the filamentation of the species to form the biofilm. The fungal biofilm protects the pathogen from antimicrobial defenses, such as defensins, and oxidative stress. Owing to their high tolerance of antifungals and immune evasion strategies, fungal infections are difficult to treat. *Candida albicans* and *Candida parapsilosis* biofilms are reported to exhibit antifungal resistance against fluconazole, amphotericin B, nystatin, voriconazole, and others, while *Aspergillus fumigatus* biofilms are resistant to itraconazole and caspofungin drugs. *Cryptococcal* biofilms are reported to endure the effect of fluconazole and voriconazole, and biofilms of *Trichosporon asahii* display resistance to amphotericin B, caspofungin, voriconazole, and fluconazole (Fanning and Mitchell 2012). Invasive aspergillosis caused by *Aspergillus fumigatus* is characterized by a high mortality rate (Jayshree et al. 2006). Thus, biofilm-mediated infections of fungus are reported to be a major concern in various hospital-acquired infections as well as surgical infections.

4 The Current Approach to Deal with Biofilm

The biofilm formed by the microorganisms are hard to control due to the inefficacy of several antimicrobial drugs. Biofilm-mediated loss incurred in the health sector as well as agriculture is a problem that needs to be addressed. Several attempts have been made to disrupt the biofilm. Various antibiotics are used to treat biofilm-mediated infections. However, the side effects of antibiotics in the process of treatment cannot be ignored. One such antibiotic, rifampin is reported to exhibit antibiofilm activity against *S. aureus* and *S. epidermidis*; however, the risk of emergence of rifampin resistance during treatment seems to be a hindrance in the process of biofilm management. Several antibiofilm agents are small molecules or enzymes that have the potential to disrupt or inhibit biofilm. Another promising antibiofilm strategy is to modify the biomaterials used in medical devices to prevent biofilm formation (Chen et al. 2013; Schilcher and Horswill 2020). As biofilms resist the inflow of various antibiotics, an increased dose of antibiotics is often given to treat the biofilm-mediated infection. The topical application of antibiotics in surgical wounds is reported to inhibit the biofilm formation of the pathogen (Ciofu et al. 2017). Römling and Balsalobre (2012) reported that nucleotide second messengers, c-di-GMP, (p)ppGpp, and potentially c-di-AMP are major regulators of biofilm formation and associated antibiotic tolerance, and targeting the pathways could hinder biofilm of the pathogens. In cases, where traditional antibiotics fail, coating of the medical devices, vaccination against biofilms, and quorum sensing inhibitors are promising future options for the prevention and treatment of biofilm-mediated infection (Zimmerli and Moser 2012). Adopting one of the mentioned strategies may not effectively control persistent biofilms. An efficient treatment of biofilm infections requires the removal of the infected foreign bodies from the infected site, selection of an effective and well biofilm penetrating antibiotics, systemic or topical administration of antibiotics in high dosage and combinations of different antibiotic, administration of anti-quorum sensing or biofilm dispersal agents (Wu et al. 2015). Owing to the rise in antibiotic resistance, along with the collaborative process, attempts have been made to search for a potent antibiofilm agent that can effectively malfunction the resistant potential of various biofilms.

5 Role of Biosurfactant in Inhibiting and Disrupting Biofilm

Pathogenic biofilms are a global concern as they tend to increase the severity of various diseases and complicate the treatment procedure. Biosurfactant, a potential antimicrobial agent has been held high due to its reported antibiofilm activity. To portray effective antibiofilm efficacy, it is very essential that the agents are capable of inhibiting biofilm formation and disrupting preformed biofilm (Padmavathi and Pandian 2014). The pathogen cells require to adhere to the substratum to initiate the biofilm formation. Biosurfactants are reported to inhibit the biofilm adhesion of

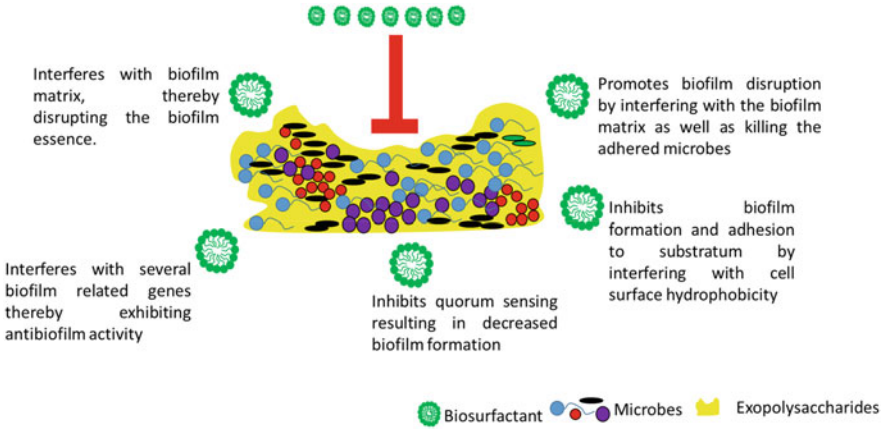

Fig. 5 Antibiofilm activity exhibited by various biosurfactant

the pathogen (Mishra et al. 2020). Adsorption of biosurfactant to the surface of the substratum changes the hydrophobicity of the cells, interfering adhesion. The inhibition of biofilm formation by biosurfactant is also established by enhanced membrane disruption, and electron transport chain inhibition, thereby restricting cellular energy demand (Satpute et al. 2016a). Several reports revealed the effectiveness of biosurfactants in interfering with the genes and the products that play an important role in the formation and maintenance of biofilm (Yan et al. 2019). The biofilm inhibition efficacy of biosurfactant can be utilized in the process of coating agents for medical implants to prevent the biofilm formation of the pathogen. Quorum sensing is reported to be an important mechanism in the process of biofilm formation, which is reported to have interfered with the presence of biosurfactants (Satpute et al. 2016a). There are also reports that the biosurfactants can modify the chemical composition of the exopolysaccharide of the biofilm. Exopolysaccharide is an important constituent of the biofilm which serves the survival strategy of the microbial community. Interference of biosurfactants with the exopolysaccharide can have a detrimental effect on the biofilm (Paraszkiewicz et al. 2021). Kim et al. (2015) reported that the interaction of rhamnolipid with protein and carbohydrate of the exopolysaccharide results in the reduction of the amide group and decrease of glucosamine respectively due to their interference in N – H bonds. The antibiofilm efficacy of several types of biosurfactant has been reported against a wide range of fungi, pathogenic yeasts, and bacterial biofilm. The antiadhesive, biofilm inhibition and biofilm disruption property of biosurfactant is facilitated by several mechanism which are summarized in Fig. 5.

6 Antibiofilm Activity Against Bacterial Pathogen

Bacterial biofilm has been a major cause of several medical emergencies in terms of infection. Several glycolipids and lipopeptides are reported to exhibit antibiofilm activity against several bacterial pathogens. Among the glycolipid, rhamnolipid, and sophorolipid are well-known for their effective antibiofilm activity against numerous pathogens. Rodrigues et al. (2006) reported that rhamnolipid applied silicone rubber inhibited 66% adhesion of biofilm produced by *Streptococcus salivarius* and *Candida tropicalis*. Glycolipid from *Burkholderia* sp. has been reported to exhibit antibiofilm activity against *S. aureus* (Ashitha et al. 2020). Biosurfactants produced by *Pediococcus acidilactici* and *Lactobacillus plantarum* were reported to exhibit antiadhesion and antibiofilm activity against *S. aureus* by regulating the expression of biofilm-related genes *cidA*, *icaA*, *dltB*, *agrA*, *sortaseA*, and *sarA* and interfering with signaling molecules (AI-2) in quorum sensing systems (Yan et al. 2019). Several studies have been carried out to establish the synergistic efficacy of biosurfactants with essential oils and antibiotics. Mukherji and Prabhune (2014) reported efficient antibiofilm activity of sophorolipid containing essential oils against *V. cholera*. *Staphylococcus* species are well-known for dwelling in several types of superficial as well as invasive infections. Several species of *Lactobacillus* are reported to produce biosurfactants, known as surface lactin or surflactin (Satpute et al. 2016b). Biosurfactant secreted by a probiotic strain, *L. fermentum* RC-14 is reported to reduce the adhesion of *S. aureus* on surgical implants, which would be effective in reducing implants-related infections (Gan et al. 2002). Pseudofactin II, a cyclic lipopeptide produced by *Pseudomonas fluorescens* is reported to decrease the adhesion of *Escherichia coli*, *Enterococcus faecalis*, *Enterococcus hirae*, *Staphylococcus epidermidis*, and *Proteus mirabilis* in glass, polystyrene, and silicone surfaces (Janek et al. 2012). Velraeds et al. (1996) reported the inhibition of adherence of uropathogenic cells (pathogen involved in urinary infection) of *Enterococcus faecalis* by 77%. Biosurfactants are reported to exhibit synergistic antibiofilm activity when combined with various antibiotics (Rivardo et al. 2011). Cell bound biosurfactant of *Lactobacillus rhamnosus* has been reported to inhibit pathogen attachment as well as disrupt the preformed biofilm of *B. subtilis*, *P. aeruginosa*, *S. aureus*, *and E. coli* cells within biofilms (Patel et al. 2021). Thus the strong antibiofilm activity of various types of biosurfactant has been reported, which provides a prospect of finding an efficient antibiofilm alternative.

7 Antibiofilm Activity Against Fungal Pathogen

The detrimental effect of fungal biofilm is reported to be far more severe than bacterial biofilm. While the fungal biofilm tends to resist the antifungal activity of several antifungal agents, several types of biosurfactants are reported to exhibit efficient antibiofilm activity against fungal biofilm. The biofilms of dermatophytes

are reported to complicate various soft skin infections. Maťátková et al. (2017) reported the synergistic antibiofilm activity of rhamnolipid and amphotericin B on the biofilm of *Trichosporon cutaneum* and *Candida parapsilosis*. Lipopeptide from entomopathogenic fungus *Beauveria bassiana* was reported to exhibit antibiofilm activity against *M. canis* (Abdel-Aziz et al. 2020). Rhamnolipid produced by *Pseudomonas aeruginosa* SS14 was reported to exhibit promising biofilm dispersive activity against *Candida tropicalis* (Borah et al. 2019). Another glycolipid called Trehalose lipid, produced by *Rhodococcus fascians* BD8 has been reported to exhibit 95% antiadhesion activity against *Candida albicans* against polystyrene surface and silicone urethral catheters (Janek et al. 2018). Sophorolipid along with amphotericin B is reported to exhibit antibiofilm activity against *Candida albicans* (Haque et al. 2017). Surfactin has been reported to exhibit antibiofilm activity against *Candida albicans* by controlling the expression of hyphal-specific genes such as HWP1, ALS1, ALS3, ECE1, and SAP4 (Janek et al. 2020). Among the several lipopeptides, the lipopeptide Iturin is reported to exhibit an antifungal impact on fungal pathogens by disrupting the cell membrane. Iturin is reported to pass through the cell membrane and interacts with the nuclear membrane and other cytoplasmic organelles membrane of the fungal pathogen (Rodrigues and Teixeira 2010). Janek et al. (2012) reported that a cyclic lipopeptide Pseudofactin inhibited 92–99% biofilm adhesion inhibition against *C. albicans* at a concentration of 0.5 mg/ml. With the decreased response of conventional antifungals against the fungal pathogen, biosurfactants can be a promising alternative with efficient antibiofilm activity.

8 Conclusion

Biofilm has a detrimental impact on several anthropological activities. Biosurfactants, with their promising antibiofilm activity, can decrease the pathogen adhesion and biofilm formation and can effectively disrupt the preformed biofilm. This facilitates the utilization of biosurfactants in food sectors to avoid the deterioration of food quality owing to biofilm-forming species. They can be of immense importance in the management of biofilm-mediated infections as well as the biofilm-oriented agricultural infections. With the emergence of antibiotic-resistant strains, the treatment of several infections has become critical. Malakar and Deka (2021) reported the antibiofilm efficacy of various biosurfactants against several bacterial as well as the fungal pathogen. Owing to their non-cytotoxicity, biosurfactant is a potent antibiofilm alternative with a promising prospect. The practical implementation of biosurfactants as an antibiofilm agent in several fields can be a biological alternative to several chemicals, that are used to get rid of the resistant biofilm.

9 Future Perspective

Biosurfactants are microbial non-toxic metabolites with an efficient antibiofilm efficacy. They can be a promising alternative to several chemical antibiofilm agents available on the market. The efficiency of biosurfactants to exhibit antiadhesive activity, biofilm inhibition, and biofilm disruption can be exploited in various fields such as biofilm repellent in biomedical applications, anti-biofouling agents, biofilm inhibitors in packaged food, etc., which would reduce the burden of chemical agents to the environments as well as would decrease the long-term toxicity caused by the chemical agents.

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