QhaliKay
REVISTA DE CIENCIAS DE LA SALUD
Una publicación de la Universidad Técnica de Manabí
ISSN: 2588-0608
https://revistas.utm.edu.ec/index.php/QhaliKay

Artículo original

Enero-Abril 2022;6(1):60-76
https://doi.org/10.33936/qkrcs.v6i1.3601

Biofilms of pathogenic bacteria and emerging antibiofilm strategies

Biopelículas de bacterias patógenas y estrategias emergentes de antibiopelículas

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Abstract

Biofilms act as physical barriers to the immune system and drugs used by the host, resulting in antimicrobial resistance. Biofilms reduce the chances of eradicating infections and can result in relapses and backsliding after conventional treatment. Biofilms have a big impact on food safety in the food industry; many foodborne outbreaks have been linked to pathogenic bacteria that can form a biofilm. Biofilm-associated infections can cause not only severe symptoms but also serious side effects and even death. The findings of an experimental study of pathogenic bacteria like Pseudomonas aeruginosa, Salmonella enteritidis, *and* Staphylococcus aureus *forming biofilms are presented in this article. The process of biofilm formation and its development phases were displayed with preserved architectonics using light and scanning electron microscopes. The amount of biofilm formed was influenced by the growth medium as well as the incubation conditions and time. Biofilm-forming microbes are a common cause of complicated and recurrent diseases, and they are usually linked to multidrug-resistant bacteria, which account for nearly 80% of all refractory nosocomial infections. Medical device- and tissue-associated biofilm infections are two types of biofilm infections. Understanding the pathogenesis and factors that contribute to biofilm formation, as well as the disruption and dispersal mechanisms of biofilms, will aid in the development of improved anti-biofilm strategies. Overall, this literature review can serve as a single source of information about microbial biofilm formation and mitigation strategies, which could be extremely useful to biofilm researchers.*

Keywords: *biofilm; pathogenic bacteria; infection; anti-biofilm.*

Resumen

Las biopelículas actúan como barreras físicas para el sistema inmunitario y fármacos utilizados por el huésped, lo que genera resistencia a los antimicrobianos. Las biopelículas reducen las posibilidades de erradicar infecciones y pueden provocar recaídas y recaídas después del tratamiento convencional. Las biopelículas tienen un gran impacto en la seguridad alimentaria en la industria alimentaria; muchos brotes de origen alimentario se han relacionado con bacterias patógenas que pueden formar una biopelícula. Las infecciones asociadas a biopelículas pueden causar no solo síntomas graves, sino también efectos secundarios graves e incluso la muerte. En este artículo se presentan los hallazgos de un estudio experimental de bacterias patógenas como Pseudomonas aeruginosa, Salmonella enteritidis *y* Staphylococcus aureus *que forman biopelículas. El proceso de formación de biopelículas y sus fases de desarrollo se exhibieron con arquitectura preservada usando microscopios de luz y electrónico de barrido. La cantidad de biopelícula formada estuvo influenciada por el medio de crecimiento, así como por las condiciones y el tiempo de incubación. Los microbios formadores de biopelículas son una causa común de enfermedades complicadas y recurrentes, y por lo general están relacionados con las bacterias multirresistentes, que representan casi el 80 % de todas las infecciones nosocomiales refractarias. Las infecciones por biopelículas asociadas a dispositivos médicos y tejidos son dos tipos de infecciones por biopelículas. Comprender la patogenia y los factores que contribuyen a la formación de biopelículas, así como los mecanismos de interrupción y dispersión de las biopelículas, ayudará en el desarrollo de estrategias mejoradas contra las biopelículas. En general, esta revisión de la literatura puede servir como una fuente única de información sobre la formación de biopelículas microbianas y las estrategias de mitigación, lo que podría ser extremadamente útil para los investigadores de biopelículas.*

Palabras clave: *biopelícula; bacterias patógenas; infección; antibiopelícula.*

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Artículo recibido el 05-07-2021 Artículo aceptado el 26-11-2021 Artículo publicado el 28-02-2022

Fundada 2016 Facultad de Ciencias de la Salud de la Universidad Técnica de Manabí, Ecuador.

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Introduction

Biofilm is an association of microorganisms that are immovably appended to the biotic or abiotic surface, encased within an extracellular polymeric substance (EPS) matrix, which might display new character with reference to metabolic activities, organic phenomenon, rate of growth, and protein synthesis[1,2]. The EPS are composed of polysaccharides, lipids, proteins, and extracellular DNA (Table 1) and play a crucial feature within side the pathogenesis of the various microbial infections[3].

Table 1. Chemical composition of biofilm

s/n	Component	Percentage of matrix
1	Microbial cells	2.5%
2	DNA and RNA	<1-2%
3	Polysaccharides	1-2%
4	Proteins	<1-2% (including enzymes)
5	Water	Up to 97%

Biofilm production is motivated and influenced by variety of things like surface conditions, chemical and physical growth factors, cellular structures, and the other challenges. The interaction between these and other factors determines its fate[4,5], since biofilms are surrounded by high relative molecular mass EPS that connect and fix cells, these cells in biofilm can survive harsh growth conditions[5], this takes place thanks to structural and physiological change takes place after cells are attached to conditioned surfaces, with the produced structural polymeric substances acting as a barrier[6] and forestall the doorway of antibiotics and sanitizer agents (Figure 1).

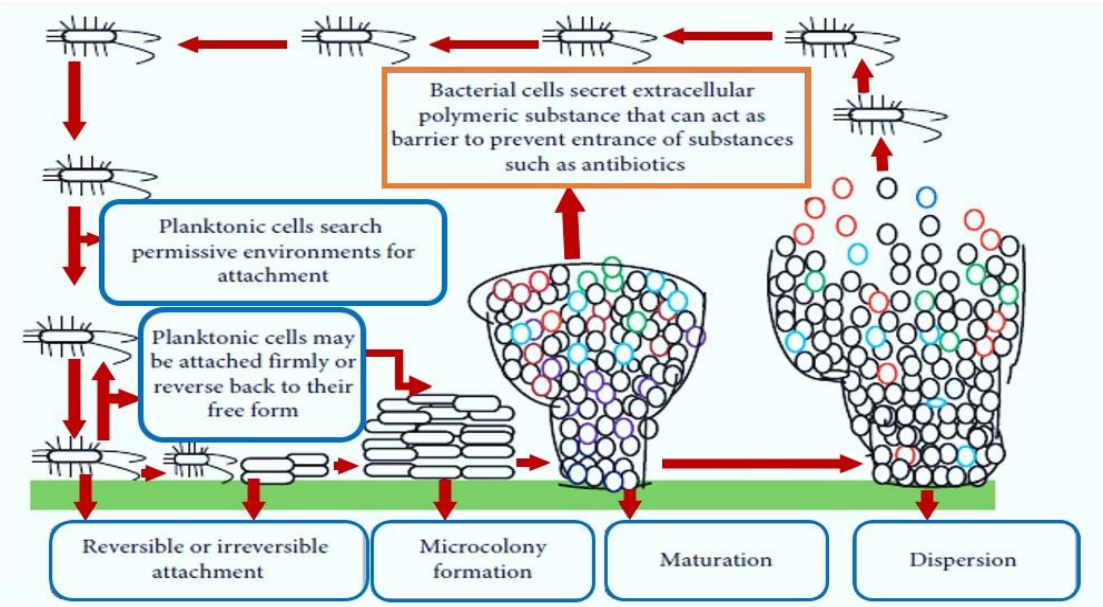

Figure 1. Biofilm formation and structure, adapted from[2,4].

It has also been reported that microbial cells within the biofilms are observed to be resistant against UV, metal toxicity, acid exposure, desiccation, pH gradients, etc.[5]. Furthermore, biofilm mode of growth induces microbial resistance to disinfection, which may lead to widespread economic and health concerns[2], for example, a search done on *Listeria monocytogenes* revealed that its biocide resistance and cap-potential to cooperate with other species forming heterogeneous communities allowed this bacterium to survive and struggle within the commercial areas[7]. In accretion to numerous physical and chemical tolerances, EPS confers immune resistance to several resident pathogenic

microbes inside biofilms with the help of using inhibiting neutrophil-mediated phagocytosis. Mosselhy et al.[8] reported that the eDNA and intercellular adhesins of EPS act as a barrier for the penetration of a range of antimicrobials. The eDNA present within the EPS chelate human antimicrobial peptides (AMPs) and reduce the antimicrobial activity of those. Pathogenic microorganisms can produce biofilm on implanted devices[9].

Many bloodstream infections and tract infections are related to indwelling medical devices which arise from biofilm consisting of bacteria embedded within an extracellular polysaccharide matrix on the surface of the catheter[2]; as an example, *Staphylococcus aureus* and *Staphylococcus epidermidis* are considered two of the foremost important pathogens, and their biofilm regularly causes device-associated infections[10]; the biofilm phenotype adapted by these bacteria during device associated infection facilitates accelerated resistance to antibiotics and host immune defences[11].

The formation of biofilm by microbial pathogens allows them to survive in hosts and causes chronic infections that achieve persistent inflammation and tissue damage[12] therefore; formation of biofilm on medical instruments, human tissues, and organs has an impression on human health and also the economy. Most bacteria and fungi, like *Pseudomonas aeruginosa*[13], *S. epidermidis*[14], *Candida albicans*[15], *Acinetobacter baumannii*[16], *Helicobacter pylori*[17], *S. aureus*[18], *L. monocytogenes*[19], *Vibrio cholerae*[20], and *Salmonella enterica*[21], are the foremost well-known pathogenic biofilm formers, these microorganisms form biofilms during a similar manner and share many common features[22,18,23].

Biofilm of pathogenic bacteria

Biofilms are important virulence factors of some pathogenic microorganisms, and a few biofilm infections seem nearly impossible to eradicate. Most bacteria and fungi, like *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Candida albicans*, *Acinetobacter baumannii*, *S. aureus*, *Helicobacter pylori*, *L. monocytogenes*, *Vibrio cholerae* and *Salmonella enterica* are good formers of biofilms and that they all form biofilms in an exceedingly similar manner with styles of common featured being shared[13,16,17,18,19,20,21].

Biofilms are one in all the foremost important health threats, causing nearly 80% of refractory nosocomial infections. Biofilm-related infections caused by pathogenic bacteria will be divided into medical device- and tissue-associated biofilm infections.

The mode of biofilm establishment in several human pathogens, in addition as its drug resistance mechanism, is well documented and reviewed by different researchers (Figure 2). This figure explains the shared mechanism of biofilm tolerance under three sections. Physical tolerance: the surplus production of EPS restricts the penetration and diffusion of antimicrobials; as a result, cells within the biofilm get longer to become tolerant.

A recent study conducted by Pavlova et al.[26], the investigator tries to research the various phases of biofilm formation and their structure by pathogenic bacteria using the strategy of growing microorganisms on coverslips in liquid and semi-liquid nutrient media with a 24 to 48 h microbial cultures within the S-form. Suspension of bacteria at an amount of 10^5 CFU/ml (according to the turbidity standard) within the amount of 5 ml was shaken employing a Vortex apparatus and introduced into Petri dishes with 20 ml of meat-peptone broth. Sterile fat-free coverslips were placed on sterile slides and immersed in a very liquid nutrient medium in Petri dishes; it absolutely was incubated in a very thermostat for 24, 48 and 72 h at 37 °C.

The coverslips were removed with tweezers and placed in Petri dishes with paper filters on the underside so as to preserve natural architectonics, it had been fixed *in vivo* by vapour of 25 you look after glutaraldehyde for 2 h. Preparations were coloured by vapour of 4 % solution of OsO_4 for 3 minutes, then an answer in style of drops was applied on the surface of a paper placed on top of a dish.

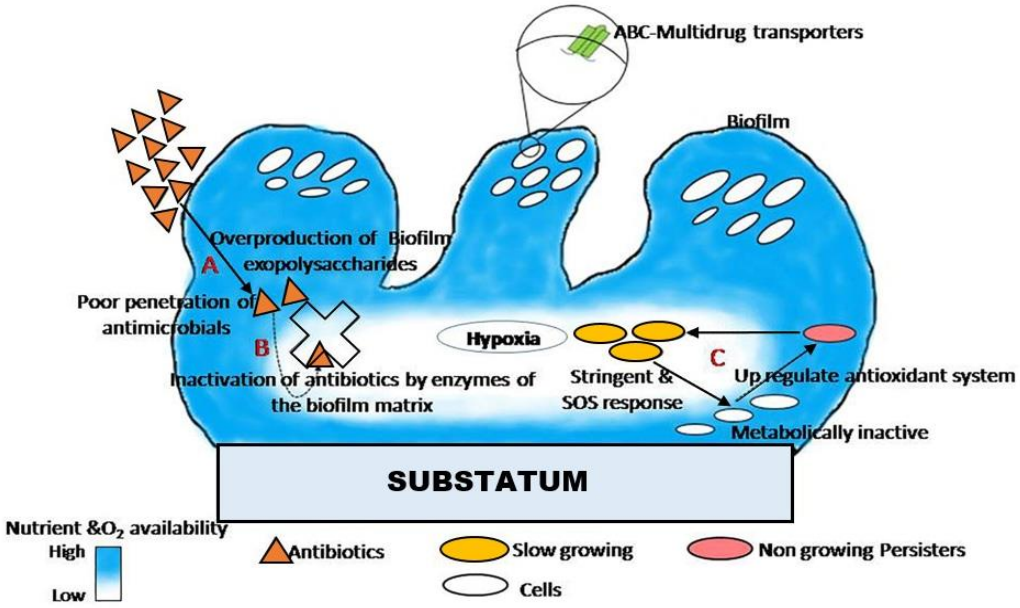

Figure 2. The final mechanism of biofilm tolerance to numerous antimicrobials. (A) Physical tolerance: biofilm matrix limits the diffusion of antimicrobials. (B) Passive tolerance: matrix enzymes inactivate the penetrated antibiotics molecules. (C) Physiological tolerance: persisted cells within the deeper layer of biofilm induce adaptive SOS (in latin, *si opus sit* = if there is need) response and thus become more tolerant[5].

After treatment with osmic acid vapors was done, the biofilms with bacteria turned yellow or yellowish-brown, these were examined employing a scanning microscope after dehydration with propylene oxide vapor and gold ion sputtering. During fixation and washing of objects in a very liquid solution, structure of biofilms undergoes irreversible changes. Bacterial morphology was examined using an AxioImager A1 optical microscope (Carl Zeiss, Germany) and a TM 4000 scanning microscope (SEM) (Hitachi, Japan).

The results on the study of the morphology of biofilm formation revealed that *S. aureus* during cultivation in an exceedingly liquid medium was seen that on the surfaces of thin coverslips, a monolayer culture represented by single bacteria within the S-form was initially formed, then clusters and biofilms were formed after 24-48 h (Figure 3). Similarly, Figure 4 shows that the expansion of *P. aeruginosa* was in the middle of formation of a dense biofilm after 48 h. In some areas, single bacteria developing on the surface are visible; this means possibility of formation of the subsequent layer of biofilm and thus a multilayer. Presence of pathogenic strains of *P. aeruginosa* in alginate causes high resistance to antibacterial and disinfectant drugs. With an outsized increase in SEM, heteromorphic cells of a spheroplastic, protoplast sort of various sizes with various manifestations of L-transformation are revealed in fragments of the population under the film and between the clusters (Figure 5). When *S. enteritidis* was examined with a scanning microscope, both single adhered bacteria and populations grouped in clusters were visible. Often channels that are involved within the metabolism and regulation of oxygen supply were identified inside the formed biofilms. Thus, using three different microorganisms, we've shown general rules of biofilm formation. Survival strategy of assorted pathogenic bacteria consists in their evolution by creation of biofilms during which bacteria are at early stages in vegetative form (S-form) with future transition to heteromorphism with various manifestations of L-transformation[26]. L-transformation process is in the course of formation of small cells with a size of 0.2–0.3 microns- stable and unstable L-forms. The latter compose 20–25 you look after the entire population. Under favourable conditions, they are reversed to their original state with preservation of pathogenicity and other biological features.

Biofilm structure can have different composition, counting on the kind of pathogenic bacteria having a particular structure of the semipermeable membrane and containing peptides, lipids and other components.

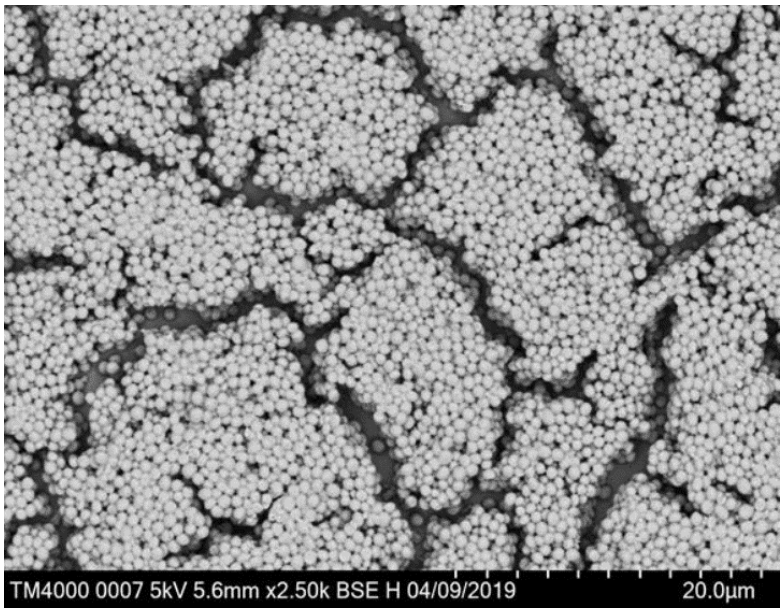

Figure 3. Formation of *S. aureus* clusters. Inside the clusters, there is a biofilm with bacteria. SEM × 2500[25].

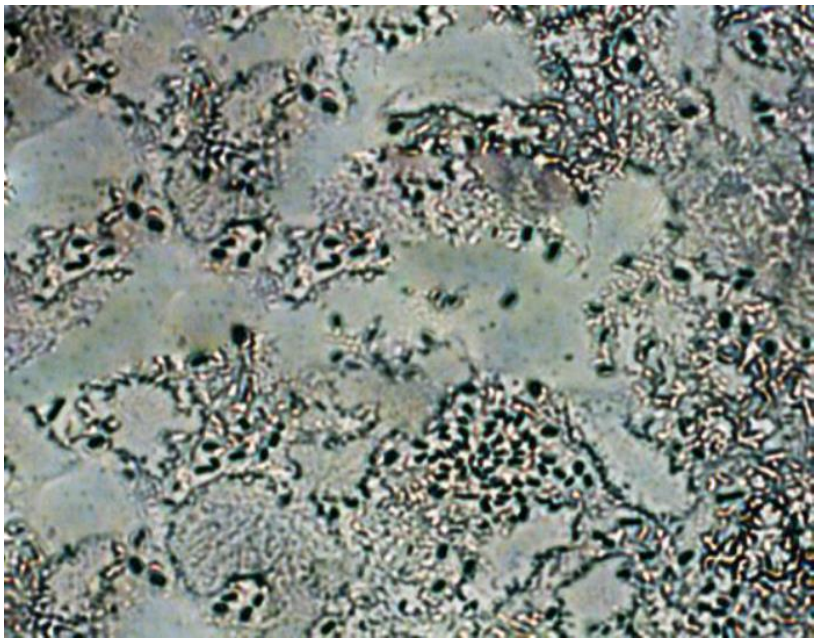

Figure 4. Formation of a *P. aeruginosa* biofilm; on the surface, there are single bacteria emerging from the film. Optical microscopy[25].

Under certain conditions, a multilayer biofilm may develop. This process is related to emergence of single bacteria on the surface of the upper layer. Then, filamentous structures are formed by bacteria, creating clusters with an exopolysaccharide matrix during which bacteria multiply and this contributes to the formation of subsequent biofilm layer (Figure 6). Study of biofilms of gram-positive

and gram-negative bacteria indicates a sequence of phases of development and existence of bacterial populations.

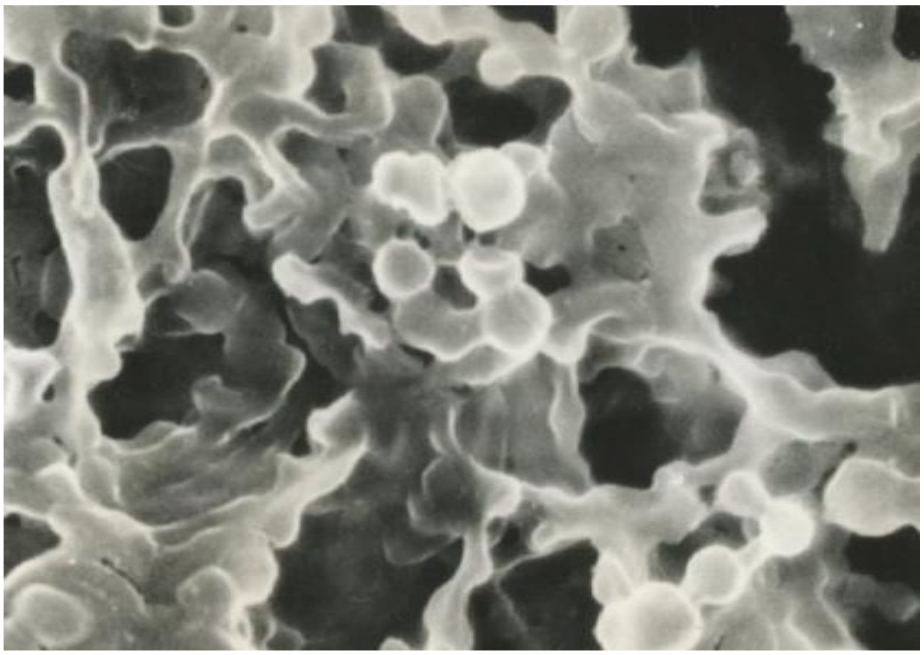

Figure 5. Fragment of formation of *S. enteritidis* clusters of spheroplast and protoplast cells included in the biofilm. SEM, ×5000[25].

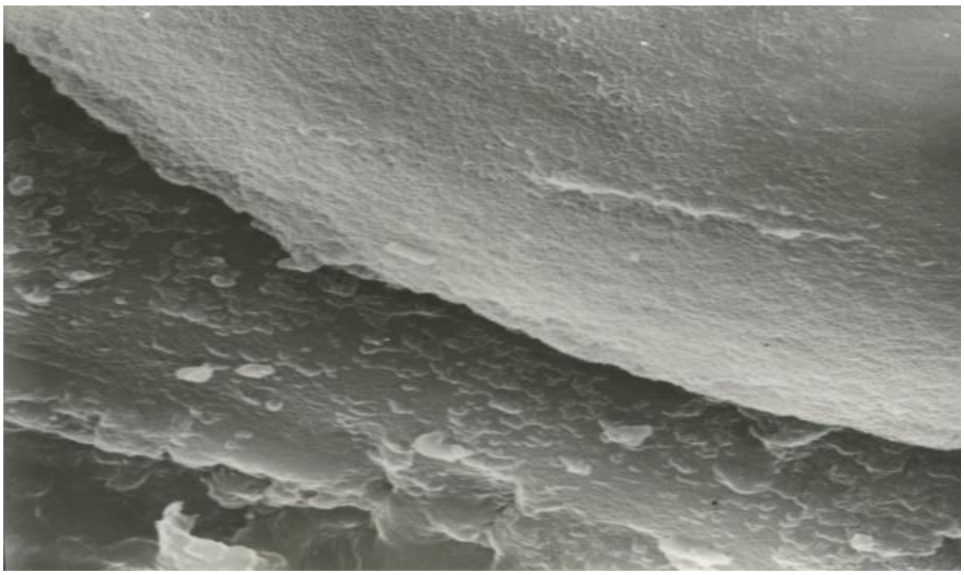

Figure 6. Multi-layer biofilm *S. enteritidis* 72 hours after cultivation. Single cells are visible on the upper layer[25].

Biofilms have a significant impact on food safety in the food industry, according to a study conducted by Joanna et al.[28], which found that pathogenic bacteria such as *L. monocytogenes, S. aureus, Escherichia coli,* and *Bacillus cereus* are dominant in retail foods and are the leading cause of food infection and disease due to their strong biofilm formation and high metabolic activity.

Drug resistance *versus* biofilm formation

Drug resistance or resistance to antimicrobial agents may be a critical problem and a significant threat to animal and health. it's imperative to grasp how bacteria develop resistance to antibiotics.

Much of our understanding of the mechanisms of antibiotic action and resistance comes from experiments during which bacteria are grown in liquid culture before being exposed to antibiotics. Yet, most bacteria in nature exist in biofilms, aggregated communities of cells encased during a matrix[28]. Biofilms represent a fundamentally different mode of life to planktonic cultures and studies have demonstrated extreme changes in gene and protein expression profiles from the identical strains when grown in liquid or as a biofilm[28]. Many infections include a biofilm component that produces the infection are difficult to treat; common examples include infections on prosthetic or indwelling devices. Biofilms are typically more tolerant to antibiotics, compared to the corresponding strain in liquid culture. One theory explaining the resistance to antibiotics of biofilms is that cells within a biofilm are metabolically inactive and a high proportion are dormant 'persisted' cells. In these dormant subpopulations, characterised by arrested macromolecular syntheses, the cellular targets that the antibiotics poison are often not essential, thus impeding bactericidal activity[29]. Despite this reduced rate, biofilms are shown to be able to adapt rapidly to changing conditions, and rapid selection of mutants with improved biofilm fitness is observed when bacteria are introduced to a replacement niche[29].

Biofilms are groups of microorganisms attached to biotic or abiotic surfaces and surrounded by a matrix composed of an EPS (Figure 7)[29]. Biofilms exist in various infections and are demonstrated to play a crucial role in human diseases, they act as physical barriers against drugs and host immune responses, resulting in resistance to antimicrobial treatment and clearly reduce the likelihood of eradicating infections which cause relapses after the standard appropriate treatment.

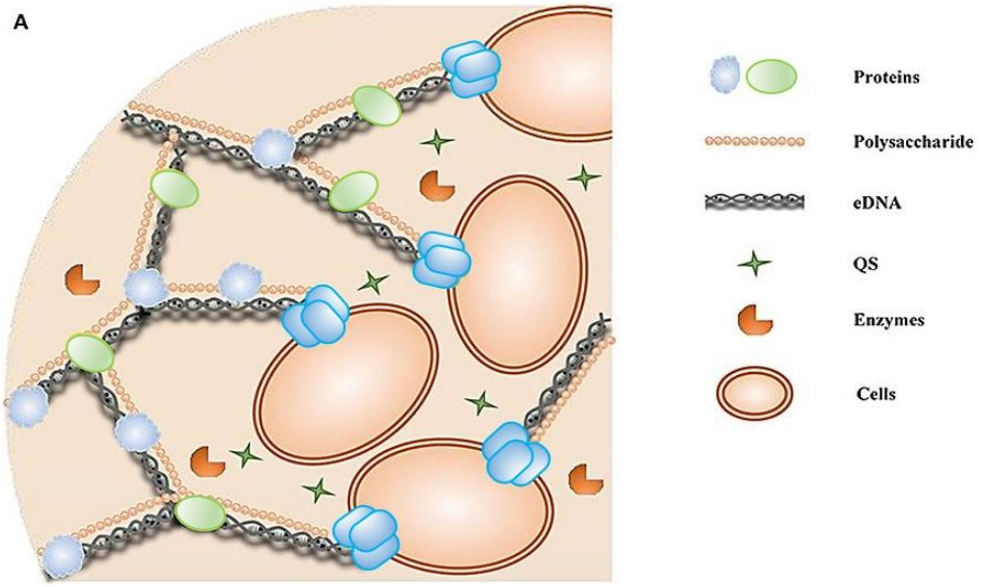

Figure 7. The structure of the extracellular polymeric substance[35]. The onset of biofilm-related infections can increase not only severe symptoms but also mortality[35]. Although more studies are that specialize in strategies to eliminate microbial biofilms, but it's better to know the roles of biofilms in infections and its mechanisms to drug resistance for this can assist in proffering solution like latest promising antibiofilm strategies (QS – Quorum sensing).

Biofilm formation

Formation of biofilm mainly involves three stages (Figure 8 and 9); the primary stage is that the adhesion stage; cells attach to a surface; within the second stage (sessile growth stage), micro-colonies are formed thanks to the assemblage of those cells. The adhesion and sessile stages of growth are reversible and therefore the cells can cluster loosely but can detach and return to a planktonic state[31] thereafter, the attached cells secrete EPS, which incorporates extracellular DNA (eDNA), polysaccharides and proteins (Figure 8) which developed into a biofilm within the third stage. This stage is irreversible, because the cells are attached within a thick and stable complex bio-molecular layer[32]. After a biofilm is totally developed, its dispersion or disassembly occurs via both active and mechanical processes, these processes occur within the fourth stage (dispersal stage). The cells within the biofilm secrete not only cell–cell-adhesive matrix components but also disruptive factors, including proteases, nucleases, phenol-soluble modulins, and regulators[33]. These disruptive factors can even promote biofilm detachment. During the method of detachment, biofilms can shed individual cells and slough off pieces into the bloodstream and also the surrounding tissues, which are related to many acute and chronic infections[34]. Cells with different phenotypes and genotypes co-express individual metabolic pathways, stress responses, and other distinct biological properties within the biofilms. A number of these cells alter extracellular polysaccharide and organelle production and even cell morphology after they sense growth within the biofilm community. DNA transfer and genetic recombination between the multiple microbial species within a biofilm occur without direct cell–cell contact through the extracellular matrix and during this manner antibiotic resistance genes may be transferred[3,35].

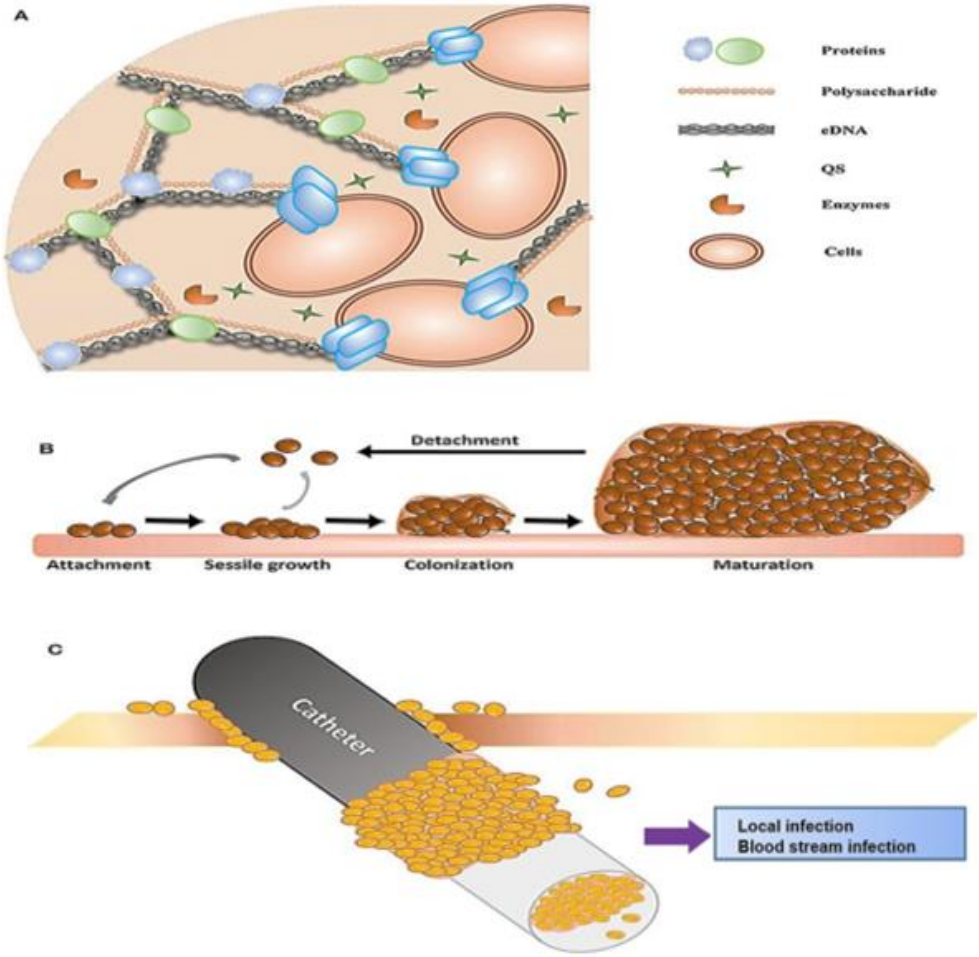

Figure 8. Schematic of biofilm formation. (A) The structure of the extracellular polymeric substance. (B) The stages of biofilms. (C) The catheter-associated biofilm[35].

Quorum sensing (QS) is a cell-to-cell communication process that controls and facilitates biofilm formation in many bacterial and fungal species, resulting in antibiotic resistance and the production of virulence factors[36,37,5,28]. QS is widely recognized as essential for genetic regulation and population dynamics and plays vital roles in biofilm development. In order to optimize metabolic production, microorganisms use QS to regulate population density[38]. By inhibiting the synthesis of matrix compounds or the degradation of the matrix in a coordinated manner[39], QS controls not only the maturation but also the disassembly of the biofilm community.

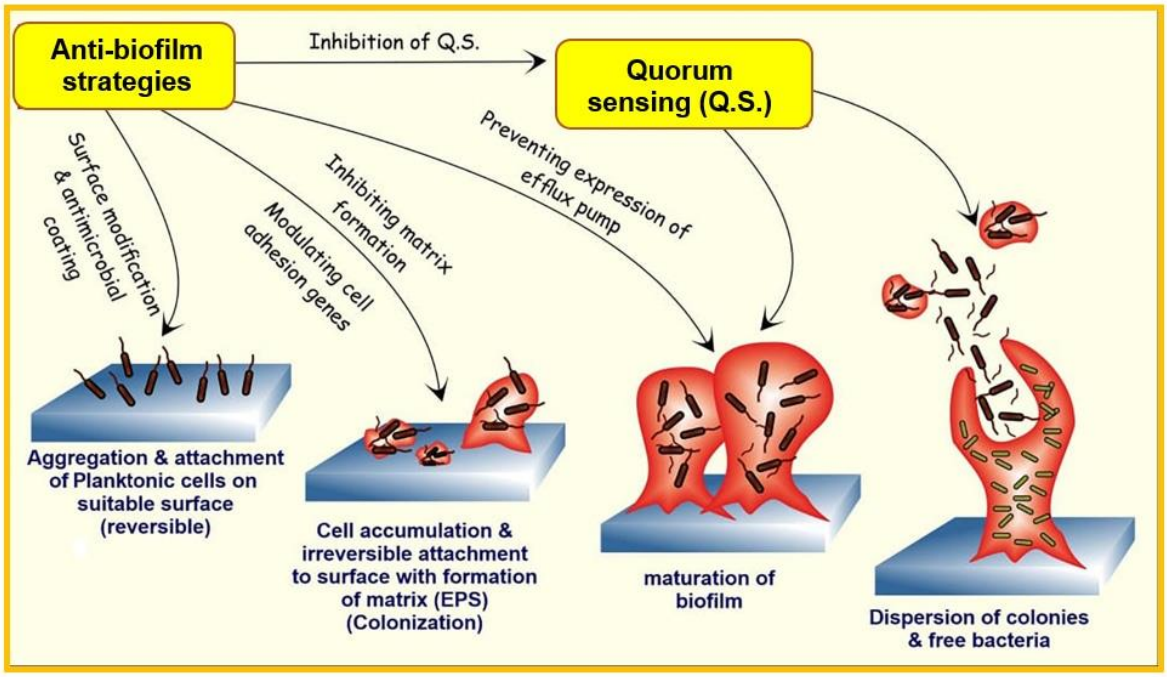

Figure 9. The stages of biofilm formation and role of QS[5].

Bacteria attach to matrix-forming proteins in humans via peptidoglycan structure, either covalently or non-covalently. With the attachment and aggregation of a sufficient number of cells, the EPS matrix is formed, and the attachment is now resistant to external repulsive forces. As the biofilm matures, the cells within the bulk structure begin to communicate and secrete specialized proteins and DNA, and some of these proteins and DNA are involved in the formation of the efflux pump. Finally, the dispersion of free planktonic cells from the formed biofilm promotes the formation of new biofilms in the periphery.

Mechanisms of biofilm resistance to antimicrobial agents

The mode of growth of biofilm gives protection against many biocides and antibiotics; thus, biofilms are hard to regulate and ultimately eradicate. It's been indicated that microorganisms re-suspended from biofilms are distinctly more resistant than planktonic cells, while the cells inside biofilms are more resistant than those re-suspended from biofilms. Biofilm cells are a minimum of many times more immune to antibacterial agents than planktonic cells (up to 1,000-fold increase)[32]. Biofilms protect cells from desiccation, chemical perturbation, invasion by other bacteria, and killing by immune cells by acting as shelters or physical barriers[40].

There are multiple mechanisms by which biofilm cells create increased resistance to antibiotics, and these mechanisms are distinct from those in planktonic cells (Figure 10). Impeded antibiotic penetration into biofilms was initially proposed to be responsible; however, penetration by some antimicrobial agents, like ciprofloxacin and fluconazole, throughout biofilms doesn't decrease[41]. It's now well-known that the matrix mesh size is far larger than the scale of antibiotic molecules[42]. The

penetration of antimicrobials into a biofilm depends on the thickness of the biofilm, the reactivity and diffusion of the agent within the biofilm, the sorption of the biofilm, and therefore the dose concentration of the agent[43]. the assembly of an exopolysaccharide matrix reduces the activity of some antibiotics, like fluconazole, in *C. albicans* biofilms, the eDNA is considered one in every of the foremost important contributors to the resistance of biofilms to antimicrobial agents, by reducing the activity of antibiotic through creating cation-limited conditions, inducing modification of lipopolysaccharide (LPS), and impairing the uptake of antibiotics, like aminoglycosides[34].

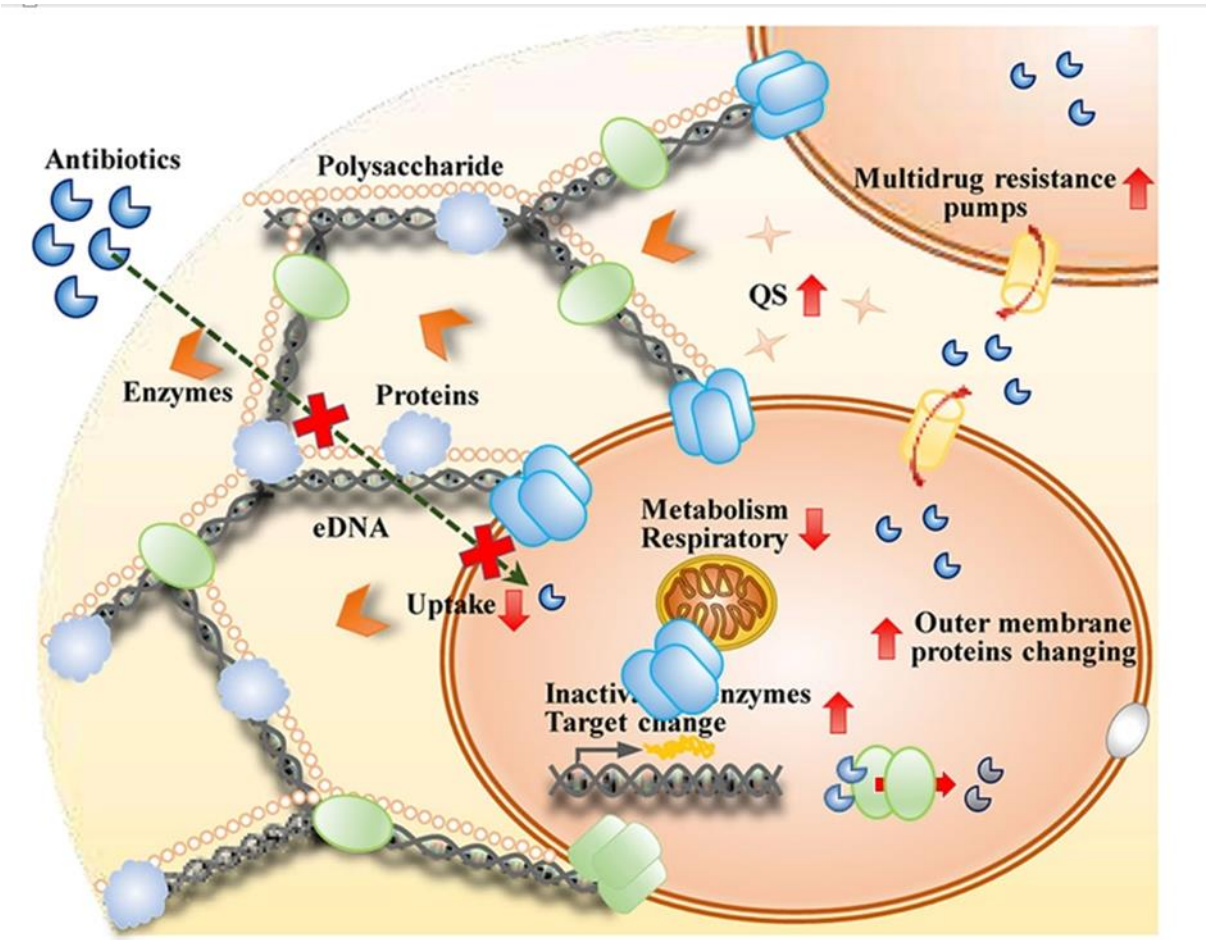

Figure 10. Mechanisms of biofilms that are resistant to antibiotics therapy[35].

It is widely accepted that the status of the cells within biofilms is related to their sensitivity to antimicrobials. The upper osmolarity conditions, greater oxygen limitations, higher metal ion concentrations, and lower pH levels within a biofilm are confirmed to be chargeable for the expression of some genes and help determine a number of the phenotypes of biofilm cells[34]. The concentration of oxygen within a biofilm is higher at the surface and lower at the underside and also the centre with cells having high level of metabolic activity located at the surface of the biofilm while those with a coffee level of metabolic activity and slow growth are found within the canter. Metabolically active cells are able to sense environmental changes and actively reply to the presence of antimicrobial stress. However, majority of the cells inside biofilms are in a very dormant state and within the stationary phase, which implies that these cells are metabolically inactive and not growing. Cells within the stationary phase within a biofilm do not grow and respire and are more tolerant to antimicrobials[43]. Changed nutrient environments and inhibition of growth within the biofilm result in increased drug resistance within biofilms.

Intrinsic mechanisms of resistance are present in biofilms, but many studies have indicated that the synergy of acquired and adaptive mechanisms contributes to antibiotic resistance in biofilms[44].

Genetic adaptation within biofilms helps cells adapt to their surroundings and increases their antibiotic resistance. Changes within the outer membrane proteins of the cells within biofilms contribute to antibiotic resistance via the expression of multidrug resistance genes. Some antibiotics can induce resistance-related enzyme expression within the cells within biofilms. As an example, high-level imipenem resistance is said to increased beta-lactamase expression induced by imipenem in *P. aeruginosa* biofilms. Piperacillin also can induce beta-lactamase expression in biofilms; however, the increased beta-lactamase expression isn't as high because the imipenem level

Biofilm persistence in chronic infections is primarily due to a combination of increased beta-lactamase expression and other protective biofilm growth mode properties[34]. Drug resistance is exacerbated by changes in multidrug efflux pump activity in biofilms. The biofilm cells' activated efflux pumps have gotten the most attention[45]. Persister cells, which make up the majority of cells in biofilm communities when they are stationary, are dormant microbial subpopulations that are phenotypic multidrug-tolerant variants rather than genetic variants[46]. The acquisition of multidrug resistance genes by horizontal transfer, which contributes to the evolution of biofilm cells, is another mechanism of antibiotic resistance in biofilm cells. QS plays a critical role in horizontal cell-to-cell communication within biofilms. Evidence suggests that biofilms have evolved these mechanisms as a general stress response that causes microorganisms in the biofilm to react to environmental changes[47,34]. Novel biofilm-fighting strategies that target these mechanisms must be developed.

Emerging anti-biofilm strategies

Biofilms can be removed by three different mechanisms, such as desorption, detachment and dispersal[48]. Reversal phenomenon of bacterial attachment is called as desorption, for instance, leaving of surface attached cells from the substratum and subsequent entry into bulk fluid. Detachment can be described as passive dislocation of biofilm embedded cells, and detachment usually happened when biofilm structure is disrupted by external forces. Whereas in biofilm dispersion, biofilm embedded cells are actively disseminated from the biofilm, which usually happened when any changes occurred in the environment. Recently, several biofilm mitigation strategies have been emerged to overcome the biofilm-based problems in different areas, and thus the biofilm control in different environmental media is one of the active research areas. Biofilms were found to be controlled successfully by using different strategies, such as ionic lipids[49], electrochemical treatment[50], photocatalytic graphitic carbon nitride-chitosan composites[51], phenol derivatives[52], bioactive glycolipids[53], ultrasound treatment[54], magnetic nanoparticles[55], quorum quenching[56], combination of high intensity ultrasound and chlorine dioxide[57], combined ciprofloxacin and azithromycin free and nano formulations[58], novel phage ZPAH7[59], tea polyphenols[60], etc. However, there is no single universal method of biofilm control in different environmental media. In addition, most of the above-mentioned strategies have been tested against one given environment, and most with model strains. Therefore, in depth insights are necessary to know the complete scenario of biofilm formation, such as EPS functional groups[61], quorum sensing[62] and quorum quenching[63], mixed culture behaviour[64].

In the recent past, there is much attention on the control of *P. aeruginosa* biofilms as this is one of the potential multi-drug resistance human pathogen. In this direction, several anti-biofilm agents have been emerged against *P. aeruginosa*, such as phytochemicals, nanoparticles, metal chelators, enzymes, antimicrobial peptides, antibodies, bacteriophage cocktails, plant products (e.g. isothiocyanates and organosulfur compounds)[65]. However, use of combination of agents giving better results, for instance, 10 nm AgNPs (silver nanoparticles) and aztreonam were found to decrease 98% of biomass and 50% reduction in the thickness biofilm of *P. aeruginosa* PAO166. Similarly, AgNPs along with colistin displayed enhanced antibiofilm properties than colistin alone. Nonetheless, for the establishment of a sustainable antibiofilm strategy for the control of *P. aeruginosa* infections, more *in vitro* and *in vivo* studies are necessary[65].

Biofilm mitigation is a becoming a challenging, which is attributed to the complexity in the biofilm formation potential of different environmental isolates. Especially in industries, biofilm mitigation is of great importance, as biofilms cause significant economic loss by various reasons such as corrosion followed by deterioration of equipment, increased fluid resistance, etc[67]. Also, biofilm contamination in the food industries can show negative effects on the quality of food products. Similar effects are also appeared in the paper industry, where biofilm formation affect the final quality of the paper[68]. Another great concern associated with the biofilm formation is human health and innumerable species of bacteria and fungi capable of producing biofilms and subsequently cause potential health disorders in the humans. It is widely known fact that control of bacteria in its sessile growth phase is much harder than bacteria in a free-floating state. Thus nowadays, several mathematical models have been emerged[66,67] to know the key roles of QS, multi-species interactions, antimicrobial resistance, mechanical properties of extracellular matrix; such insights are expected to provide in depth understanding of what properties of biofilms support the bacteria embedded with in a competitive edge against treatment. Mathematical models are also available to strengthen the idea of how to prevent the unwanted biofilms in different environmental facilities such as food and water[69]. It is also important to note that the interaction of biofilm cells with surface is vary depending on the architecture of the biofilm. In monolayer biofilms, cell-to-surface interactions are much important than interactions between the constituent cells (cell-to-cell)[70]. In fact, bacterial external structures (e.g. flagellum and pilus) are the key structures accelerate the rate of formation of the monolayer biofilm. But bacterial cells tend to produce multi-layered biofilms when dual interactions are involved, such as cell-surface and cell-cell interactions[71]. In addition, during the formation of multilayer biofilms, there is a masking and neutralization of repulsive forces of negative surface charges by means of one of several mechanisms such as mutations, down-regulation of the O antigen encoding gens, additional of divalent cations, synthesis of EPS[70]. These types of mechanistic insights are very helpful in the design or search of a sustainable biofilm mitigation strategy.

Quorum sensing inhibitors (QSI) are another choice of biofilm mitigation agents. They found to be effective in the control of both growing biofilm and established biofilms[72]. Cyclic dipeptides (e.g. cyclo (L-Pro-L-Val)) and others (e.g. cyclo (L-4-iodo-Phe-L-Pro), cyclo (L-4-chloro-Phe-L-Pro)) are potential QSIs, and effectively mitigate the LuxR-based based QS activities such as biofilms and luminescence in modelled bacteria, e.g. *P. aeruginosa*[73] and *Vibrio fischeri*[72], respectively. Importantly, QSIs have a capacity to inhibit biofilms of not only the bacteria but also fungi; for example, biofilms of *C. albicans* have been mitigated by several types of QSIs like farnesol, farnesoic acid, tyrosol, tryptophol, and phenylethyl alcohol[74]. Farnesol is very effective in controlling the later stages of biofilm development in *C. albicans*, where germ tube formation and hyphal-inducing conditions are badly affected by farnesol[75]. Like farnesol, sesquiterpene alcohol farnesol is also known to block the yeast to hyphal switch and biofilm formation in *C. albicans*[76].

Conclusions

Biofilms are sessile microbial cell communities embedded in an EPS, forming a matrix which adhere to surfaces of medical implants and wounds, to periprosthetic tissue and enables cell to cell adhesion and aggregation, leading to the formation of flocs. The matrix consists of bacterial secreted polymers, mostly, exopolysaccharides, lipids, proteins, and extracellular deoxyribonucleic acid (e-DNA); which aids the intricate three-dimensional (3D) structure and excessive resistance or tolerance against drug in bacteria. The e-DNA could prompt the expression of resistance genes and the horizontal gene transfer between bacterial cells within biofilms.

Conflicts of interest

The author declare that there is no conflict of interest.

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