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Review Article

Biomolecules for early detection of biofilms through point-of-use devices

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ABSTRACT

Biofilms are communities of microorganisms that attach to biotic and abiotic surfaces. They cause infections and industrial contaminations that carry along serious health issues and great economic loss. The secreted extracellular polymeric substances enhance biofilm tolerance to antibiotics, biocides and host defenses. Therefore, there is an urgent need to develop new strategies for detecting and monitoring microbial biofilms in the early stages of formation. Biosensor technology can provide rapid detection, high selectivity and sensitivity using small, portable, simple, and low-cost devices. The selection of an appropriate molecular target involved in a regulatory network during different stages of biofilm formation determines the type of information the biosensor provides. This comprehensive review discusses the biomolecules that contribute to the formation of biofilms, with a particular emphasis on those involved in the initial stages, and their potential as specific targets for the early detection of these microbial structures. Additionally, we provide a critical analysis of the current state of biosensors for detecting biofilms, including recent work with rapid test based on lateral flow immunoassays (LFIA). The information analyzed in this review could guide the development of innovative biosensors or chemical sensors to detect the early formation of biofilms, contributing to the fight against antimicrobial resistance.

1. Introduction

Biofilms are a complex biological system of microbial colonies that are embedded in a polymer matrix composed of polysaccharides, proteins, and extracellular DNA (eDNA) which can be attached to different surfaces. Generally, it has been considered that biofilm formation is a strategy for bacteria cells to protect themselves under unsuitable conditions. By producing biofilms, the resistance of bacterial cells to antibiotics and antimicrobial agents increase about 1000 times more than their planktonic form [1–3]. They are responsible for the biofouling of membranes and surfaces in industrial settings such as water treatment and food industry. In the medical field, they are at the origin of many nosocomial infections due to contamination of medical devices or prosthesis [1,2]. It has been estimated that over 80 % of infections are related to biofilm formation [1,4–6]. These healthcare and economic problems have triggered the need for improving the detection of biofilms. In addition, biofilms have also been found at the International Space Station, particularly at the water recovery systems. In this context, there is also an increasing interest on their early detection, by means of simple devices that could be taken on space missions, with low or even no power consumption [7].

Biofilm monitoring and detection methods could be classified as direct and indirect methods. Direct measurements are related to the mass or the cell density, whereas indirect measurements are related to the estimation of metabolic activity and products, including gases or liquids [8,9]. A recent review highlights the potential of scanning electrochemical microscopy as an emerging and versatile technique for fundamental studies on biofilm formation, cell adhesion and antimicrobial coatings [10]. Biofilm detection by biological methods involve culture and molecular biology techniques. Enumeration methods rely on

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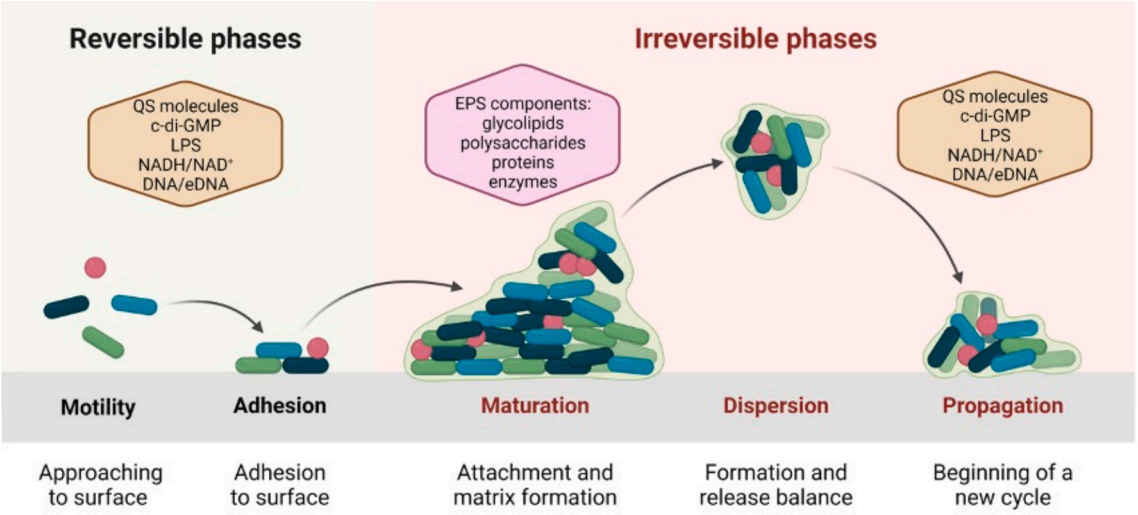


Fig. 1. Biofilm formation process and the molecules that may be detected at each stage. (2022). Retrieved from Adapted from "Biofilm Formation Cycle", by BioRender.comhttps://app.biorender.com/biorender-templates.

cultures and colony-forming units (CFU) identification. However, sometimes a fraction of bacteria may grow slowly or not grow at all, and bacteria could be viable but non-culturable. Molecular biology techniques such as polymerase chain reaction (PCR) and quantitative PCR (qPCR) are mostly used in biofilm characterization studies. These methods have higher sensitivity and specificity than culture techniques. However, this approach can detect non-viable microorganisms due to the presence of eDNA and DNA derived from dead cells [11,12]. The aforementioned methods are time-consuming, labor-intensive, and require expensive instruments and specialized staff. Therefore, analytical tools that allow for early-stage detection and monitoring of the development of biofilm formation in real-time [13,14] are essential, for instance, to minimize and prevent bacterial infection caused by biofilms formed on medical devices, or to guarantee safety at surfaces for food processing.

Sensor technology could offer rapid detection, high selectivity, and high sensitivity using small and low-cost devices. Indeed, bacterial biosensors have attracted much interest in many applications, such as healthcare, where rapid decisions on bacterial infections could be taken at the point of care. Additionally, for environmental monitoring and agro-food industrial settings the use of sensors is crucial for the application of efficient protocols for surface cleaning and safety [15,16]. This positively contribute to the One Health multidisciplinary approach adopted by the World Health Organization (WHO), which acknowledges the interconnection among human, animal, and environmental health [17,18].

Biofilm detection is still a challenging problem because analytical methods need to improve the specificity, sample treatments and analysis requirements (for instance, *in vivo* or *in vitro* analysis in the clinical field). The chemical species produced in different steps of biofilm formation could be considered as targets for biofilm detection and monitoring. Even though, the capacity for early detection is also related to limit of detection of the biomolecular species accessible at each stage. Other reviews in the literature have focused on electrochemical transducers [19], spectroscopic characterization techniques [20], or general analytical methods to detect the emerging threat of antimicrobial resistance [21]. A general review classifying biofilm sensors according to their purpose (dynamic studies, biofilm formation and biofilm-based

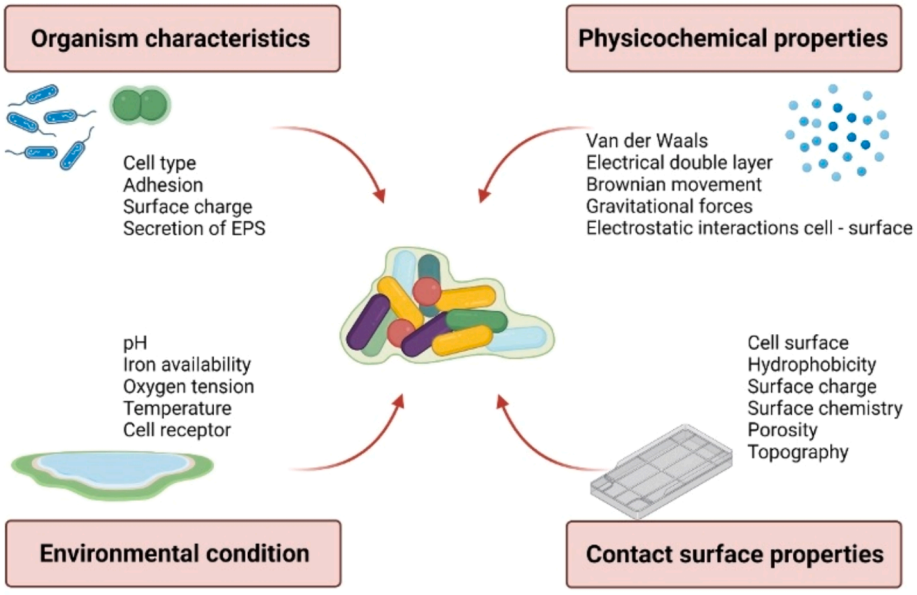
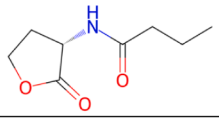
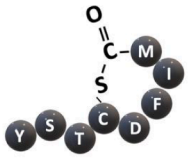
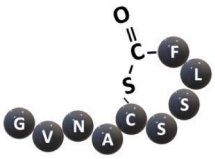
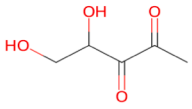
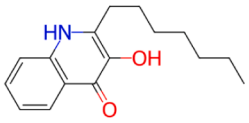
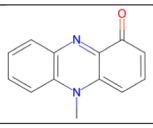
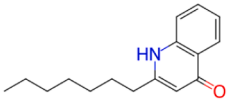


Fig. 2. Factors that have an influence on biofilm formation by bacteria cells. Created with BioRender.com.

Table 1
Signaling molecules involved in bacterial QA. (A) N-acylhomoserine lactones (AHL) signaling molecules family. N-3-butanoyl-L-homoserine lactone (C4-HSL) in *P. aeruginosa* sp. (B) Autoinducing peptides (AIPs) signaling molecules family. Types I and II. (C) Autoinducer −2 (AI-2) signaling molecules family. R-THMF (*Salmonella* sp.) (D) Other types of signaling molecules (*Pseudomonas* quinolone signal (PQS), Pyocyanin, and 2-heptyl-4-hydroxyquinoline (HHQ). Chemical structures were obtained from Chembel (https://www.ebi.ac.uk/chembl/).

(A): AHL family	C4-HSL: N-(butanoyl)-L-homoserine lactone	
(B): AIP family	autoinducing peptide-I (AIP-I)	
	AIP-Π: autoinducing peptide Π	
(C): AI-2 family	4,5-dihydroxy-2,3-pentanedione (DPD)	
(D): Others	*Pseudomonas* quinolone signal (PQS)	
	Pyocyanin	
	2-heptyl-4-hydroxyquinoline (HHQ)	

sensors) has also been recently published [22].

In this review, we have followed a different approach, summarizing and discussing the biomolecules produced at different stages of biofilm formation that can serve as targets for detection. Then, recent advances in biosensor design that focus on specific analytes for early biofilm detection were discussed. A simple and fast detection method is through lateral flow immunoassay (LFIA), and a discussion on recent studies based on LFIA for the detection of biofilms is included. This information may be valuable for analytical chemists who are aiming to develop new tools for early biofilm detection. From a One Health perspective, efficient and early detection of biofilms could be beneficial in reducing the usage of antibiotics and, consequently, the risk of antimicrobial resistance. This perspective involves collaborative efforts across health science professions to optimize health outcomes for people, animals, and the environment. It recognizes that antimicrobial resistance often arises from the overuse of antibiotics in human, animal, and environmental sectors. By adopting a holistic approach that includes infection prevention, improved sanitation, and responsible antimicrobial use, we can effectively curb antibiotic misuse and mitigate the spread of resistance. Many countries and international agencies have embraced the One Health approach in their antimicrobial resistance action plans. Within this framework, early biofilm detection plays a crucial role in our broader efforts to combat antimicrobial resistance [23].

2. Biofilm formation

Biofilm formation and dispersal are highly controlled processes that result in a complex population of bacterial cells through several steps (Fig. 1). It starts when planktonic bacterial cells detect specific environmental signals that trigger the transition to sessile form [6]. The next step is when bacterial cells come into contact to a surface, initiating the sensing process through extracellular and intracellular signaling [24]. This strongly depends on the characteristics of the microorganism, environmental conditions, and physicochemical surface properties. Bacterial cells attach to the solid surface by physical forces including gravitation and diffusion or extracellular adhesive organelles such as curli, fimbriae (or pili), flagella, lipopolysaccharide (LPS) and surface proteins [6,24–28]. Therefore, cell surface hydrophobicity has also a role on biofilm formation in species such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli* [28] by controlling the initial surface interaction with both biotic and abiotic surfaces.

Fig. 2 shows the factors affecting the initial adhesion of bacteria to surfaces. Although initial attachment is reversible, bacteria start to develop microcolonies through cell proliferation and to produce a surrounding matrix known as extracellular polymeric substance (EPS). The EPS comprises various components, including polysaccharides like alginate, *Pseudomonas* exopolysaccharide Pel, and *Pseudomonas* exopolysaccharide Psl, as well as proteins, nucleic acids (eDNA and eRNA), lipids, lipopolysaccharides, and other biopolymers. Remarkably, EPS can constitute up to 90 % of the biofilm mass [29]. EPS plays a pivotal role in irreversibly anchoring bacterial cells to surfaces, offering protection to these cells against various stressors, including antibiotics, antimicrobials, oxidative agents, and host immune responses [6,28,30–32]. EPS also protects the signaling molecules of quorum

sensing (QS), extracellular enzymes, and metabolic products from the environmental conditions, and also supports cell to cell communication of bacteria [28]. Following initial adhesion and EPS formation, the biofilm development process enters the maturation phase, marked by continued bacterial growth and additional EPS production to support the bacterial cells [6,28,33]. Last, mature biofilms shed bacteria, microcolonies, and biofilm fragments, which disseminate to the surrounding environment and return to the planktonic state. It is believed that biofilm dispersion is crucial for the diffusion and self-renewal of bacterial communities [26,28].

3. Selection of analytes for early biofilm detection

As we stated before, the specific time to consider an early biofilm is dependent on species/strain and environmental conditions where is growing. However, the main differences between early and mature biofilms are relative to biofilm structure: the initial attachment and the formation of microcolonies is observed in early biofilms, whereas in mature biofilms there are complex, three-dimensional structures with multiple layers; the extracellular matrix (EPS matrix) is partially developed in early biofilms and abundant in mature biofilms; resistance (mature biofilms exhibit significantly higher resistance to environmental stresses compared to early biofilms); and cell differentiation (mature biofilms show cellular differentiation, with varying metabolic activity and the presence of persister cells, which are typically absent in early biofilms).

At each stage of biofilm formation, a wide range of biomolecules are produced and secreted (Fig. 1). In fact, biofilm development is regulated at the genetic level and requires the expression of different factors in response to environmental and physiological signals [6,28,34]. Therefore, these biomolecules may be target analytes for the detection of these complex bacterial communities, even at early stages of their formation.

For early detection, the biomolecules that have been used for the design of biosensors include signaling molecules for QS molecules and c-di-GMP. Other molecules are also discussed. In addition, we have considered including planktonic cells as targets for biofilm detection. They can serve for early detection and for confirming the effectiveness of a treatment for biofilm removal. As bacterial cells are shed in the later stages and they return to planktonic state, their detection is a suitable approach to determine if biofilm dispersal to surrounding areas has taken place.

3.1. Quorum sensing (QS)

The first messenger in the regulation of biofilm development is the QS system. QS system is a cell-to-cell communication process that allows bacteria to regulate gene transcription and group activity in response to cell density [35–37]. While the QS system is not directly involved in attachment and biofilm initiation, these processes are essential for the development of biofilm. Moreover, QS is recognized as the primary regulator of biofilm dispersal [6,28,38]. In addition, QS can regulate other bacterial activities such as antibiotic resistance, bioluminescence, and expression of virulence factors, mediated by extracellular signaling molecules called autoinducers (AI). These are produced and secreted during bacterial growth and retained by EPS [37,39]. When the concentration of signaling molecules reaches a threshold level, they induce phenotypic effects by regulating target gene expression. The nature of signaling molecules and QS systems varies with the type of bacteria [28]. N-acyl homoserine lactones (AHLs) are chemical compounds that are produced by more than 70 species of Gram-negative bacteria, including *P. aeruginosa* and *E. coli* [40,41]. In Gram-positive bacteria, peptides are produced as signaling molecules which are called auto-inducing peptides (AIPs) [42]. Table 1 shows the structure of some of signaling molecules, which play a role in bacterial QS and are involved in processes such as biofilm formation, virulence, and metabolism [42].

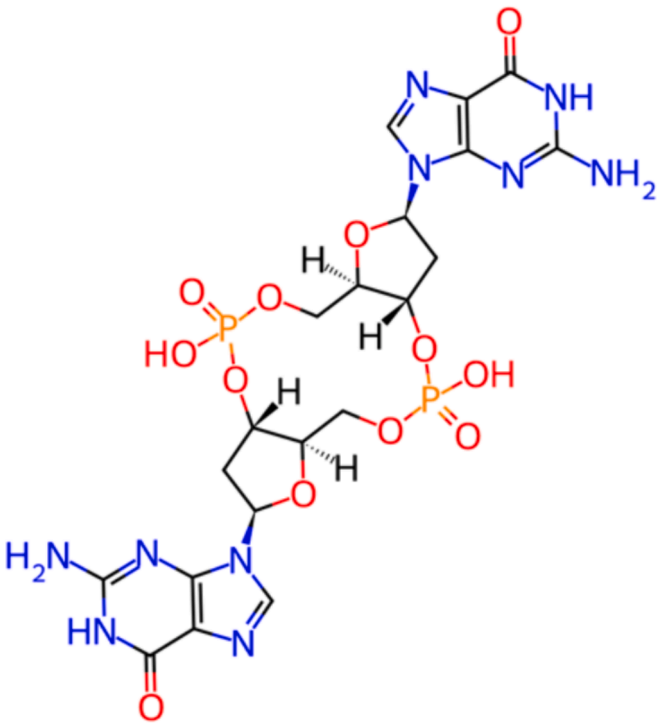


Fig. 3. Chemical structure of c-di-GMP molecule. Chemical structure was obtained from Chembel (https://www.ebi.ac.uk/chembl/).

3.2. C-di-GMP

C-di-GMP, the intracellular secondary messenger (Fig. 3), regulates various processes such as the transition between planktonic and biofilm forms and links the information of environmental conditions sensed by the cells to the gene regulators in many bacterial species: *P. aeruginosa*, *P. fluorescens*, *Salmonella typhimurium*, and *E. coli* [28,34,38,43,44]. The concentration of c-di-GMP is strongly regulated by diguanylate cyclase (DGC) and phosphodiesterase (PDE) enzymes, which synthetize and degrade c-di-GMP, respectively [45]. High levels of c-di-GMP activate the biofilm formation through the inhibition of different types of motilities and the synthesis of matrix exopolysaccharides and adhesins. On the contrary, low c-di-GMP content down regulates the biosynthesis of adhesins, polysaccharides, and leads to increased bacterial motility and biofilm dispersal [6,34,46]. During biofilm maturation, the second messenger regulates exopolysaccharides and surface protein production as extracellular matrix components in biofilm formation [47]. There is a connection between QS system and c-di-GMP and their integration allow bacteria to sense information about the cell population density within the c-di-GMP signaling network [36,48].

3.3. Other biomolecules

Other biomolecules with the potential to be considered as targets for biofilm detection include nicotinamide adenine dinucleotide (NADH), which is commonly used to monitor bacterial growth and proliferation. Polysaccharides, glycolipids, secreted proteins, and enzymes, including cellulose and alginate, are among the initial biomolecules secreted during early biofilm formation and play a significant role in surface adhesion and biofilm structure [49,50]. Actually, these biomolecules are major components of the EPS that contribute to the firm adhesion of the biofilm to the surface and to the maintenance of the structure of the EPS matrix. The eDNA and eDNA binding proteins are also components of the EPS and play an important role in the first steps of adhesion and aggregation [51], in the stability and integrity of the biofilm, and the protection from antibiotics and detergents [52]. Sensors that could

Table 2
Biomolecules that could be considered as a biofilm-specific biomarkers for detection of biofilm and some model organisms.

Target	Microorganism	Biomolecules name	Location	Function	Ref.
Bacterial cell	All bacteria species	–	Cell and biofilm-associated	Biofilm production agent	[55]
DNA	All bacteria species	Deoxyribonucleic acid	Cell and biofilm-associated	Genetic information of bacteria	[56]
QS signalling molecules	Wide distribution in bacteria species	AHLs family, AIPs family, and AI-2 family	Secretion during biofilm formation and development	Regulation of gene expression to the production of polysaccharides, virulence factors, biofilm development	[57]
Second messenger	Wide distribution in bacteria species	C-di- GMP	Secretion during biofilm formation and development	The secretion and regulation of biofilm formation and development	[45]
Polysaccharides	*E. coli*	Cellulose	Extracellular matrix	Surface adhesion, contribution in biofilm structure, cell-to- cell binding, cohesion, resistance to shear force stress, stability, providing properties of elasticity	[58]
	P. aeruginosa	Psl	Extracellular matrix/ cell- associated	Surface adhesion, contribution in biofilm structure, stability, cell-to- cell binding, protection against immune response	[59]
		Pel	Extracellular matrix/ cell- associated	Surface adhesion, contribution in biofilm structure, stability, cell-to- cell binding, protection against antibiotics	
		Alginate	Extracellular matrix	Surface adhesion, contribution in biofilm structure, stability, cell-to- cell binding, promotes adherence, protection against environment	
	S. aureus	Polysaccharide intercellular adhesion (PIA) or poly N-acetyl glucosamine (PIA/PNAG)	Extracellular matrix	Surface adhesion, promotes adherence, contribution in biofilm structure, stability, protection against antibiotics	[60]
Proteins	*E. coli*	Biofilm surface protein (CsgD)	Cytoplasmic membrane/ Extracellular	Surface adhesion, cell-to-cell binding	[61]
		Curli (CsgA and CsgB protein)	Extracellular matrix	Surface adhesion, adhesion to surface, cell-to- cell binding, cohesion, development of the biofilm structure, resistance to shear force stress, stability, providing properties of elasticity	
	P. aeruginosa	Biofilm surface protein (SadB)	Cytoplasmic membrane/ Extracellular	Surface adhesion, cell-to-cell binding, contribution in biofilm structure, stability	[62]
	S. aureus	Biofilm associated protein (BAP),	Extracellular matrix	Surface adhesion, cell-to-cell binding, contribution in biofilm structure, stability	[63]
		Biofilm surface protein (SasG)	Cell-associated/ extracellular matrix	Surface adhesion, cell-to-cell binding	[64]
Virulence factor	*P. aeruginosa*	Pyocyanin	Cell-associated	promoting cell-to-cell interactions between cells, redox active toxin	[31,65,66]
Nucleic acids	Wide distribution in bacteria	eDNA	Extracellular matrix	Biofilm structure, adhesion–cohesion, nutrient source, gene transfer	[31,67,68]
		RNA	Extracellular matrix	Gene expression regulation, adhesion	
Lipopolysaccharide	Wide distribution in Gram-negative bacteria	Endotoxin	Cell-associated / extracellular matrix	surface adhesion, toxicity of gram-negative bacteria, colonization, host invasion, establishment and durability of biofilms, activation of immune response, and antibiotic resistance,	[31,69]
Adenine dinucleotide	Wide distribution in bacteria	NADH	Cell-associated	Oxidation NADH to NAD+could be an appropriated target for the detection of growing bacterial biofilm	[70]

detect the secreted DNA by bacterial cells may constitute a good approach for early biofilm detection [53]. Regulatory small RNAs (sRNA) control various physiological processes by binding to target mRNAs or proteins, including biofilm formation [54].Table 2 shows biomolecules secreted by bacterial cells that could be considered as target analyte or biofilm biomarker. The correlation of their presence with the different steps during biofilm formation can be found at Fig. 1.

3.4. Detection of planktonic cells

As previously mentioned, planktonic bacteria could be also considered as a target for monitoring and early detection of biofilm [71]. A rapid detection of bacteria able to form biofilm, even if they have not started yet, is critical for industrial and clinical settings. It is a suitable approach to confirm rapidly the effective removal of biofilms after treatment with detergents or anti-microbial compounds. It may be useful to analyze surrounding areas by means of checking the presence or absence of dispersed bacteria that have returned to the planktonic state. The selection of the surface proteins in bacterial cells as a biomarker would allow getting specific information about the bacteria species or serotype or specific proteins for bacterial adhesion. This approach offers some advantages over DNA-based detection methods, which do not discriminate between biofilm and planktonic bacteria. Detection of planktonic cells must consider that the expression of surface proteins can vary depending on the bacterial species and growth conditions, and therefore a careful selection and validation of the biomarker is necessary for an accurate detection [72,73].

From a most general point of view, the detection of planktonic bacteria has been undergoing important changes and exploring different technologies [74]. For instance, DNA/RNA or peptide aptamers offer several advantages over traditional antibody reagents, such as stability and a longer shelf life, therefore they are considered as promising recognition elements for bacterial membrane antigens and toxins [75]. Also, bacteriophages and their associated endolysins have shown

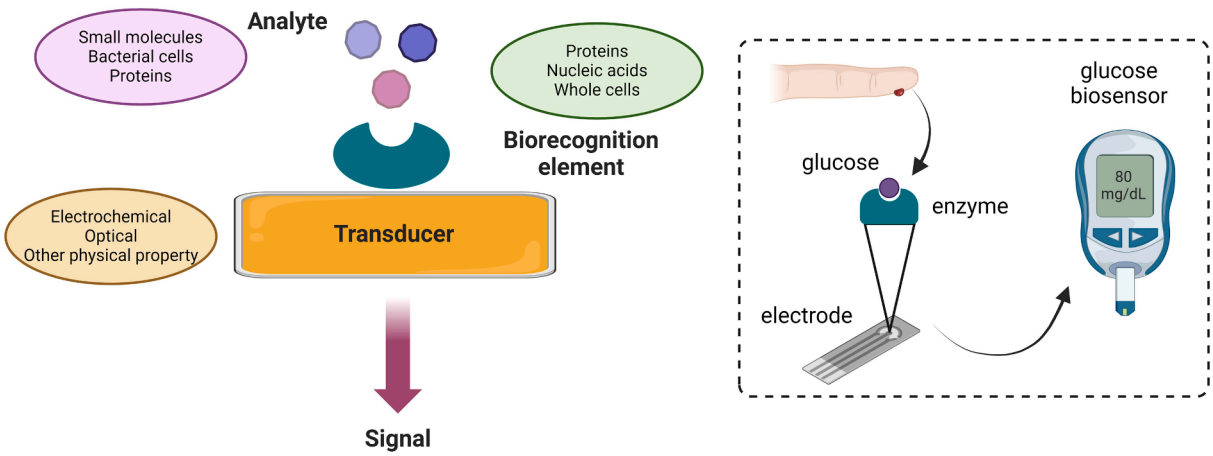


Fig. 4. Basic elements with examples of a typical biosensor on the left. On the right, an example of biosensor with the main components. Created with BioRender.com.

Table 3
Biosensors developed for detection of autoinducer molecules, toxins, and c-di-GMP.

Analyte	LOD / linear detection range	Reference
pyocianin	100 nM	65
oxo-C12-HSL	2 pM (liquid cultures)	79
	14 pM (artificial saliva)	
AHL	10 – 120 nM	81
Autoinducer-2 (AI-2)	400 nM – 100 μM	83
DMHF	0.66 nM	86
C4-HSL	0.54 nM	
C6-HSL	0.88 nM	
C8-HSL	0.72 nM	
N-3oxo-C6-HSL	0.68 nM	
3-O-C12-HSL	0.5 μM	87
Pyocianin	500 nM	88
Pyocianin	95 nM	89
c-di-GMP	50 nM	90
c-di-GMP	30 fmol	92

potential as highly specific bioreceptors for the detection of bacterial cells or biomolecules in various diagnostic applications, including the detection of biofilms [76].

4. Biosensors that could be used for early biofilm detection

A biosensor (Fig. 4) is a small size analytical instrument that can provide specific quantitative or semi-quantitative analytical information by using a biorecognition element coupled with a transducer. The response of the biosensor is a signal directly or indirectly related to the presence of a target analyte. Biosensors are usually classified according to the recognition element or the transduction mechanism [77,78]. In the next sections, biosensors for the detection of QS molecules and c-di-GMP are discussed (Table 3). Some of the biosensors reported in this section have been designed to detect bacteria cells, or to carry out fundamental studies of biofilm formation. However, these studies would be also very relevant for early detection of biofilms.

4.1. Biosensors for autoinducer molecules and toxins

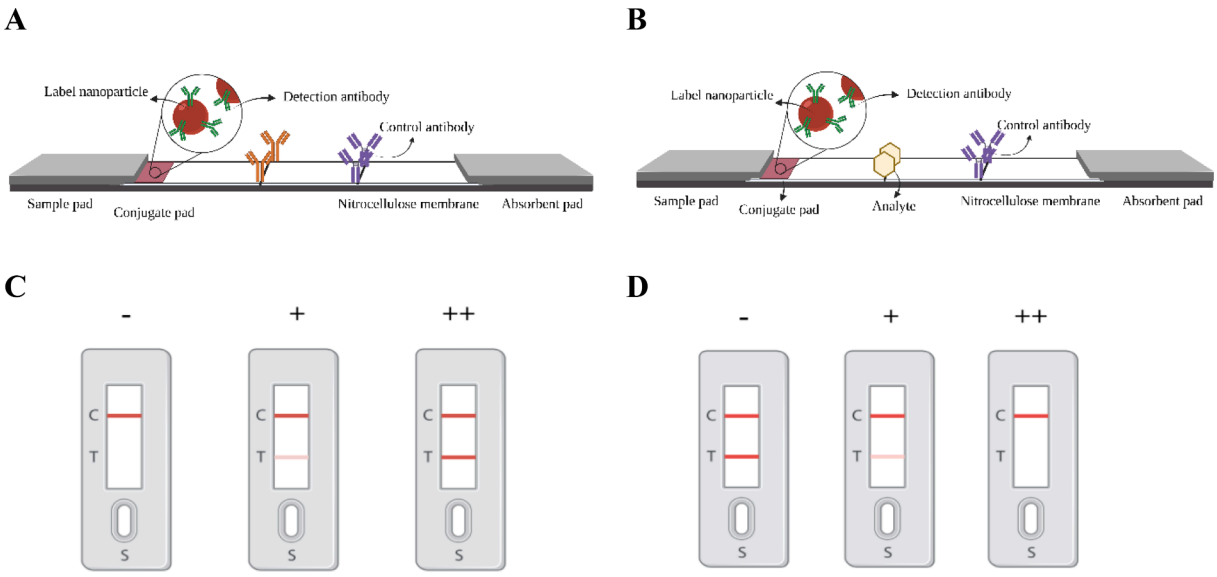
A sensor for detecting signaling molecules (AHLs and AIPs) as target would have the advantage of covering a wide range of species. Baldrich *et al.* [79] developed an electrochemical biosensor to detect AHLs indirectly using a reporter gene under the control of a quorum sensing promoter in *Agrobacterium tumefaciens* NTL4 (pZLR4) strain. Other work developed a rapid and sensitive electrochemical sensor using differential pulse voltammetry at a boron-doped diamond electrode for detecting *P. aeruginosa* PA14 signaling biomolecules (PYO, HHQ, and PQS) to enable early biofilm detection and clinical management of *P. aeruginosa* in cystic fibrosis patients [80]. AHLs were detected in artificial urine media, as a model of urinary tract infections (UTI), with good specificity and sensitivity data [81].

Due to the fact that autoinducer molecules are low molecular weight compounds, they are also low immunogenic, therefore, most devices rely on direct measurement of their physicochemical properties rather than the use of specific antibodies for their detection [82,83]. These methods could be adapted to point-of-care devices, although immunosensors for autoinducer molecules are scarce up to date. In some cases, the difficulty of obtaining recognition elements with suitable affinity and selectivity has been overcome by using molecularly imprinted polymers (MIPs) [84,85]. Habimana *et al.* [86] developed a new type of artificial receptor based on a combination of quantum dots and MIPs that can detect and quantify AHLs in real bacterial supernatant samples with satisfactory recoveries. Aptamers against homoserine lactone (HSL) have also been developed and tested for inhibition of the growth of *P. aeruginosa*. In related research, an electrochemical aptasensor was developed to detect N-3-oxo-dodecanoyl L-homoserine lactone (3-O-C12-HSL) [87], which is a type of HSL characteristic of QS in *P. aeruginosa*. Overall, the main challenges for detection of biofilms through autoinducer molecules would include the need to improve the limit of detection and the development of effective sampling protocols. Remarkably, most of the work has been carried out with electrochemical transducers, i.e., low-cost devices, suitable for miniaturization, and with possibilities to adapt the design to different surfaces and substrates.

Pyocyanin is a toxin and virulence factor, which also plays an important role in biofilm formation, promoting cell-to-cell interactions [66], and it is also considered a specific electroactive biomarker for *P. aeruginosa*. Several studies used this molecule for detecting and monitoring the biofilm formation of this bacterium. For instance, Liu *et al.* [65] developed an electrochemical biosensor chip for the long-term cultivation of biofilms and in-situ monitoring of pyocyanin. Other work considered this biomarker for *P. aeruginosa* detection in a biofilm culture using a polyaniline/gold nanoparticles-decorated ITO electrode as a biosensor [88]. Alatraktchi *et al.* [89] developed a simple and inexpensive approach based on a novel paper-based electrochemical biosensor for the detection of pyocyanin.

4.2. Biosensors for c-di-GMP

The detection of c-di-GMP with high sensitivity and selectivity was already achieved by a simple, label-free, self-assembled biosensor. The detectable concentration of c-di-GMP ranged from 50 nM to 1 μM with a detection limit of 50 nM [90]. Dippel *et al.* [91] designed the first



Scheme 1. A) Lateral flow test, sandwich format. B) Lateral flow test, competitive format. C) Test results for positive and negative samples of a sandwich assay. D) Test results for positive and negative samples in a competitive assay. Created with BioRender.com.

chemiluminescent biosensors for studying c-di-GMP signaling networks in bacterial cells and lysates, particularly in complex environments such as gastrointestinal tracts, soil, and plant surfaces. In a complementary study, this technology was improved by developing a ratiometric, chemiluminescent biosensor that selectively responds to c-di-GMP with the aim of visualizing c-di-GMP levels in real time during the stages of host infection [92]. An important step forward was reached by the development of an RNA-based biosensor for detection of c-di-GMP under anaerobic conditions, which is important for understanding the role of this second messenger in bacterial physiology and pathogenesis [93]. All these sensors have been developed to detect c-di-GMP, and while their primary focus has not been on biofilm detection, they possess the potential to be considered for such applications.

4.3. Multichannel biosensing

The concept of multichannel biosensing refers to the analytical method of using multiple sensing channels within a single device to simultaneously detect multiple analytes or biomarkers or study the specific interactions with different components at once. Typically, each channel operates independently to detect different targets, providing a more complete, comprehensive and conclusive profile of the sample.

This approach enhances the efficiency, sensitivity and specificity of the biosensors, something that is particularly relevant for complex biological systems such as biofilms, that can have different species and different EPS profiles. As such, this approach holds potential for the development of more precise and complex systems for early detection and monitoring of biofilms, reducing false positive, increasing sensitivity and the number of potential applications. The fact that a single device can measure more analytes at once translates into an enhanced applicability for different types of biofilms, each with a specific EPS composition, while also enabling to discern between the different species present in the biofilm.

Multichannel biosensing has been effectively used for the detection of bacteria and the identification and discrimination between different species. In 2022, Wang *et al.* [94] reported a multichannel sensor array for bacterial identification that relies on the interaction between the bacteria and polyethyleneimine (PEI)-based polymers, which were labelled with different fluorophores. Specific interaction of each bacterial species with the different PEI complexes delivered a particular fluorescence signal, enabling successful discrimination. Similar techniques have been reported by, Liu *et al.* (2017), Phillips *et al.* (2008) and by Han *et al.* (2017) [95–97].

This approach has also been successfully applied to the detection and analysis of biofilms. Ngernpimai *et al.* (2019) [98] developed a multichannel sensor array-based poly(oxanorborneneimide) (PONI) polymers as the scaffold. These PONI polymers incorporate one recognition element which showed selective binding to biofilm matrices (EPS) and one environmentally sensitive fluorescence transducer, delivering a total of six output channels. This technique takes advantages of the selective interactions between the sensors and the components in the biofilm matrix, to discriminate and classify biofilms. Additionally, the authors validated its applicability in a wound infection model.

Another example was reported in 2014 by Li *et al.* [99]. They developed an AuNP-based multichannel nanosensor for the rapid identification of bacterial biofilms, also exploiting the interactions between AuNPs conjugated with fluorescent proteins and the EPS in biofilms. The principle is similar to the other examples mentioned above, disruption of these conjugates upon interaction with the EPS components restores fluorescence, creating distinct patterns that allow for the differentiation of various bacterial biofilms, generating a multichannel fluorescence response unique to each type of biofilm. The sensor was tested on biofilms formed by six different bacterial species: *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. The effectiveness of the sensor was further validated in an in vitro wound model that included a mixed culture of bacterial species and mammalian cells, specifically human fibroblasts.

5. Possibilities offered by lateral flow immunoassays (LFIA) in the detection of biofilms

LFIAs, also known as immunochromatographic strip test [100], are an excellent example of popular PoCT systems which are inexpensive, sensitive, and specific for early detection of planktonic and sessile cells in these sectors [101]. The technical basis of the LFIAs was derived from the latex agglutination assay, was developed in 1956 by Plotz and Singer [102,103]. One clear example of first successful and marketable product emerged the pregnancy test in the 1970 s, utilizing the identification of human chorionic gonadotropin (hCG) in urine [103]. Another notable instance of its utilization occurred during the global COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2

Table 4
LFIA platforms developed to detect bacterial cells.

Analyte	LOD	Reference
Stx2a	0.1 ng/mL	104
E. coli O157:H7	100 cells/mL	105
E. coli O157:H7	10^2 CFU/mL	108
E. coli O157:H7	9×10^2 CFU/mL	109
E. coli O157:H7	100 CFU/mL (in buffer) 600 CFU/ mL (in liquid food systems)	110
E. coli O157:H7 S. typhimurium	50 cells /mL	111
Cell wall peptidoglycan of *S. aureus*	10^6 CFU/mL	112
Surface protein A of *S. aureus*	10^7 CFU/mL	113
P. aeruginosa	2.41×10^4 CFU/mL	114
L. monocytogenes *S. aureus*	10^5 CFU/mL 10^3 CFU/mL	115
S. aureus *P. aeruginosa* S. typhimurium	10 cells /mL	116
S. aureus	2 CFU/mL	117
F. tularensis LPS	5 ng/mL (visual LOD)	118
B. cereus	10^4 CFU/mL	119
MRSA S. aureus	1.1×10^2 CFU/mL	120
Salmonella Enteritidis	7 CFU/mL	121
Listeria phage A511	10^7 CFU/mL (in 2 h)	122

(SARS-CoV-2) in 2020–2021 [104–106]. Traditional LFIA combines chromatography and immunoassay techniques on a nitrocellulose membrane. Typically, this method offers information about the presence or absence of a target analyte by inducing a color change in the test and control lines (TL and CL) on the membrane within minutes of starting the assay [107]. This line represents an immunoassay featuring immobilized recognition elements, such as antibodies or aptamers (Scheme 1). The TL is designed for the specific identification of the target analyte, while the CL serves to validate the test. They are a good alternative to conventional methods, mostly due to their easier handling and fast in obtaining results. Although LFIAs cannot be strictly considered sensor technology because there is not a recognition element on direct contact with a transducer, the TL at the nitrocellulose membrane could be coupled to different transducers to give rise to a novel generation of biosensors. A recent review in the literature summarizes the progress towards LFIA-based electrochemical sensors [108].

In this section, we provide an overview of recent development of LFIAs to detect bacterial cells that are critical in the food industry and in the clinical environment (Table 4).

The characteristics of LFIA technology make it suitable to be used in the detection of few numbers of cells and consequently, it could be applicable for early biofilm detection. There are several examples about the use of LFIA in the detection of important pathogen bacteria such as shiga toxin-producing *E. coli* (STEC), which causes serious gastrointestinal diseases through foodborne contamination. Rapid and sensitive detection of these strains may contribute to improve food safety [109]. In this sense, the shiga-toxin 2 (Stx2) was detected by LFIA in bacterial cultures and food matrices [110]. A surface-enhanced Raman scattering (SERS)-based LFIA biosensor was developed for the sensitive and quantitative detection of *E. coli* O157:H7 in biological samples, including tap water, milk, human urine, lettuce extract, and beef with a low limit of detection (LOD) of 100 (cells/mL) [111]. This technology can be even coupled to a smartphone-based reading platform with the goal of accurately and objectively determining bacterial cell concentration in food matrices based on color intensity [112]. A gold superparticles (GSP) based LFIA was developed for detecting *E. coli* O157:H7 in milk [113]. In related research, a novel method for ligand exchange on gold nanorods (AuNRs) was developed to enhance the efficiency and sensitivity of LFIA. This method has achieved a remarkable LOD, with the ability to detect bacterial concentrations as low as 1×10^2 (CFU mL^{-1}) [114]. Han *et al.* [115] improved the sensitivity of LFIA for detecting *E. coli* O157:H7 by using Pd-Pt nanoparticles as a nanozyme probe and applying the 3,3′,5,5′-tetramethylbenzidine (TMB) substrate onto the test line. A recent study proposed a plasmonic enhanced lateral flow sensor (pLFS) for rapid and sensitive detection of *E. coli* O157:H7 in low numbers using liposome encapsulating reagent to trigger the aggregation of gold nanoparticles (GNPs) and generate a colorimetric signal [116]. In a related investigation, researchers developed a fluorescent LFIA using silica-quantum dot nanobeads (Si@DQD) as the advanced fluorescent tag for the simultaneous quantification of *Salmonella typhimurium* and *E. coli* O157:H7 [117].

Targeting the cell wall peptidoglycan of *S. aureus* with specific antibodies that recognize this molecule was the strategy employed to design an immunochromatographic test for rapid detection of this pathogen in respiratory samples of asthmatic patients [118]. Other work used the surface protein A of *S. aureus* for its detection in blood samples [119]. Antibodies targeting *Pseudomonas aeruginosa* were used to develop a LFIA suitable for food and water samples, common reservoirs of this bacterium [120]. The traditional sandwich format of a LFIA may be modified to enable simultaneous detection of pathogens. Vancomycin was coupled to the reporter label to detect Gram-positive bacteria and antibodies were used at the test lines to capture *Staphylococcus aureus* and *Listeria monocytogenes* [121]. Multiple detection of bacteria in complex samples can also be achieved by means of a SERS-LFIA approach, with LOD of around 10 cells mL^{-1} for *S. aureus, S typhi,* and *P. aeruginosa* [122].

Novel biorecognition elements previously mentioned can also be used in LFIA platforms. The use of multivalent aptamers combined with nanoparticles with enzyme-like activity was successfully applied in a LFIA for detection of *S. aureus* with enhanced sensitivity (down to 2 CFU mL^{-1}) [123]. LPS was used as biorecognition element to develop a rapid and efficient diagnostic platform for the detection of *Francisella tularensis*, which causes tularemia and needs to be diagnosed early [124]. The cell wall binding domain (CBD) of a phage endolysin was used as recognition element to detect *Bacillus cereus* [125], a microorganism that grows in food processing settings and is highly resistant to high temperatures or chemical treatments. A similar approach was used to detect methicillin-resistant *Staphylococcus aureus* (MRSA) a [126] pathogen associated to delayed wound healing. Bacteriophages showed similar performance to that achieved by using antibodies in a lateral flow platform for detection of the foodborne pathogen *Salmonella enterica* serotype Enteritidis [127]. The study conducted by Stambach *et al* [128] involved the combination of a LFIA with SERS for the detection of *Listeria monocytogenes* using the A511 bacteriophage.

Additionally, LFIA has gained recognition as an essential tool in combatting antimicrobial-resistant (AMR) bacteria. The widespread dissemination of AMR bacteria is a significant public health issue, and detecting and identifying their resistance mechanisms remains a complex task. Ideal diagnostic tests should offer swift, cost-effective outcomes to facilitate deployment in any microbiology laboratory. LFIA aligns with these criteria and has emerged as a pivotal resource for tackling AMR [129]. The study conducted by Moguet *et al.* [130] developed and validated a LFIA, known as the LFIA-CTX test, for the early and efficient detection of expanded-spectrum cephalosporin (ESC) resistance in Gram-negative bacteria. This detection method is intended to facilitate timely and effective therapy while also enabling the prompt implementation of infection control measures to prevent the spread of antibiotic-resistant strains in healthcare settings. In the other study conducted by this research group, they have focused on the detection of antimicrobial resistance in bacteria, particularly those with ESC-hydrolyzing capabilities, using a multiplex LFIA. The study aims to assess the performance of this LFIA for the early detection of ESC hydrolyzing ß-lactamases in various bacterial isolates, including those from different genera (*Enterobacter*, *Pseudomonas spp.*, and *Acinetobacter spp.*), by retrospectively evaluating its sensitivity and specificity [131].

All these works demonstrate that currently LFIA are able to detect bacterial cells with suitable limits of detection, and these methods would

Table 5
Comparison of biosensors for biofilm detection according to the choice of biomarker.

System	Strengths	Weaknesses	Potential Improvements
Biosensors for Autoinducer Molecules	– Versatile – Capable of detecting a wide range of species through autoinducer molecules – Rapid and sensitive detection of specific signaling molecules such as AHLs and AIPs	– Limited immunogenicity of autoinducer molecules may require physicochemical property-based measurements	– Enhance specificity and sensitivity for autoinducer molecules. – Develop effective sampling protocols. – Explore the use of molecularly MIPs as recognition elements.
Biosensors for c-di-GMP	–High sensitivity and selectivity in detecting c-di-GMP. – Applicable in complex environments such as gastrointestinal tracts, soil, and plant surfaces.	– Need for adaptation and validation for biofilm detection.	–Investigate adaptation of biosensors for enhanced biofilm detection. – Improve sensitivity and specificity for biofilm-related applications.
Biosensors for Detection of Planktonic Cells	–Critical for monitoring and early detection of biofilm in clinical and industrial settings. – Alternative recognition elements like aptamers and bacteriophages offer stability and longer shelf life.	– Surface protein expression variability necessitates careful biomarker selection – Requires development of specific immunochromatographic assays for accurate detection.	– Further improvement in sensitivity and specificity for planktonic cell detection. – Explore adaptation to different stages of biofilm formation. –Novel generation of LFIA based biosensors

be applicable to planktonic stage before cell attachment. However, the detection of few attached bacteria or the bacteria just before attachment to the surface would be the next challenge. This could be possible by targeting sessile membrane antigens. There is therefore a great potential to extend the use of LFIA to those cases, although this possibility has not yet been explored. This would bring along another challenge: the design of specific recognition elements for that purpose.

In this review, in the context of biofilm detection, different methods and technologies have been explored, each offering specific advantages, weaknesses, and potential improvements that are vital to consider in the pursuit of accurate and early biofilm detection. Table 5 highlights the key features of each detection system.

6. Conclusions and future trends

Biofilm formation is a complex multi-step process that results in the attachment of microorganisms to all kind of environments. These colonies secrete extracellular polymeric substances that protect them from the action of antibiotics, biocides, and host defenses. Consequently, biofilms have great impact on public health, which highlights the need to develop rapid devices for early detection in the clinical and industrial settings.

In this work, we have reviewed the literature on biofilm sensors (including LFIA) with potential for early biofilms detection. These platforms are based on biomolecules that are indicative of first stages in the formation of the biofilms, mainly autoinducer molecules, c-di-GMP, or the pyocyanin toxin produced by *P. aeruginosa*. Planktonic cells may also be suitable markers in biosensors for early detection, as they first adhere to the surface in a reversible manner. Moreover, these devices could be used to monitor an effective removal of biofilms, or to assess the possible dispersion of a biofilm to surrounding areas. Multichannel biosensing has a promising application in the field of biofilm detection. Multiple analytes can be measured with a single device, thus enabling the determination of multi-species biofilms, which are naturally found in different ecosystems.

Overall, biosensors for biofilm detection offer a wide range of advantages: great versatility, sensitivity, and applicability in complex environments, among others. The use of LFIA platforms can additionally provide novel, simple, cost-effective, and portable devices with high sensitivity for early biofilm detection. Recent LFIAs targeting bacterial cells with impact in the food industry and in the clinical environment have been discussed in this work. These tests hold great potential, as they can be coupled to transducers and become a novel and successful generation of biosensors.

Remaining challenges in this field that need to be addressed in the future are related to the development of suitable receptors for the biomarkers of interest. For instance, the low immunogenicity of autoinducer molecules may limit the development of antibodies that can be used as biorecognition elements. In this sense, aptamers, bacteriophages, or endolysins are novel alternatives to be explored in the biosensor design and further adapted and validated for biofilm detection. Biomimetic receptors, such as MIPs can overcome the difficulties raised by recognition elements with restricted affinity and selectivity. Including novel targets, such as sessile surface proteins, would also provide specific information about biofilm formation, although this field has not yet been explored.

CRediT authorship contribution statement

Shayesteh Bazsefidpar: Writing – original draft, Methodology, Investigation. **Clara Saweres-Argüelles:** Visualization, Methodology, Formal analysis. **Gemma Gutiérrez:** Writing – review & editing, Supervision, Funding acquisition. **Maria Matos:** Writing – review & editing, Supervision, Methodology. **Victor Calero:** Writing – review & editing. **Esther Serrano-Pertierra:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Pilar García:** Writing – review & editing, Visualization, Methodology. **María Del Carmen Blanco-López:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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