UNIVERSIDAD DE INVESTIGACIÓN DE TECNOLOGÍA EXPERIMENTAL YACHAY

Escuela de Ciencias Biológicas e Ingeniería

TÍTULO: Biofilm formation on the surfaces of fibers

Trabajo de integración curricular presentado como requisito para la obtención del título de Ingeniería Biomédica

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Urcuquí, Diciembre 2020

Urcuquí, 23 de octubre de 2020

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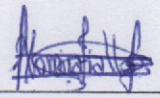

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Dedication

This thesis is dedicated:

To my parents, Jimena and Marco for their unconditional support in my life, for their teachings and for the effort they have made for me to achieve my goals.

To my sisters, Katherin and Ariana, who teach me, correct me and support me to be a better being for society.

To my friends: Andre, Dani P., Dani Q., Angie, Danna, Dani N., Bryan C., Alexis, Pau, Fer, Giorgia, Raizza, Galo and Daya C., for their company, support, for their smiles, for selflessly rooted themselves in me and even when they are not aware at all, positively marked this stage of my life.

To my tutors, Frank and Nelson for being an example of upright and responsible professionals.

Xiomira Andreina Fiallos Ayala

Acknowledgment

I want to thank God for allowing me to exist and to be formed.

To thank my tutors, Ph.D. Frank Alexis and Ph.D. Nelson Santiago for guiding me in the execution of the thesis, for their teachings and dedication.

Thanks to Marco G. and Federico S. for their significant contributions to the editing of this thesis.

Also to thank the professionals who gave me their support and knowledge when I started my project, Javier Santamaría, Eliana Lara, and Alexis Debut.

I also thank all the teachers I have had during my training, for being virtuous and dedicated people at their jobs, with a special mention to those who became my friends, Graciela S., Javier G., Francisco A., Fred H., Markus T., and Alexander L.

Xiomira Andreina Fiallos Ayala

RESUMEN

Una biopelícula es una estructura de comunidad bacteriana encerrada en una matriz como resultado de la interacción célula-célula con una superficie. El enfoque principal de la formación de biopelículas es la creación de un entorno estable y homeostático que mejora el crecimiento, la densidad de población celular y también proporciona resistencia y protección bacterianas. Cuando las biopelículas se adhieren a plantas, humanos o superficies no vivas, pueden formar una relación simbiótica, pero las bacterias patógenas pueden dejar su nicho nativo y adherirse a otros tejidos produciendo efectos adversos.

Existe una relación importante entre la superficie colonizada y la formación de la biopelícula, esta adherencia está mediada por diferentes tipos de interacciones, desde factores ambientales, interacciones fisicoquímicas, y características del material. En el caso de las fibras, que son polímeros, han surgido para actuar junto con algunos materiales o solas para crear nuevos biomateriales con fines clínicos. Cuando las bacterias colonizan esos biomateriales, representa un peligro para la salud humana, dado que las barreras de defensa están alteradas, facilitando la transmisión de patógenos, y conduciendo a bacteriemias o infecciones graves, comúnmente conocidas como enfermedades/infecciones nosocomiales o infecciones asociadas a la atención de la salud, es decir, son infecciones adquiridas en el entorno hospitalario.

Para el 2015, el Consorcio Internacional para el Control de Infecciones Nosocomiales, (CICIN) investiga que la tasa de mortalidad asociada a las enfermedades nosocomiales en el Ecuador puede llegar a 38%. Ante esto y por el impacto que tienen las infecciones asociadas a los biomateriales en los sistemas de salud pública, es importante determinar cómo es el mecanismo por el cual se forma la biopelícula. Por lo tanto, esta tesis ofrece una visión general de la adhesión bacteriana, así como de las propiedades físico-químicas, topográficas y mecánicas de los biomateriales que median o controlan la colonización bacteriana, además del riesgo de infecciones asociadas (patogénesis) que implica en un contexto de salud pública. Por último, se examinan las aplicaciones y los enfoques de las fibras naturales y sintéticas, en su mayoría asociadas para usos en el campo biomédico.

Palabras clave: biopelícula, adhesión bacteriana, patogenia, infección, fibras.

ABSTRACT

A biofilm is a matrix-enclosed bacterial community structure as a result of cell-cell interaction with a surface. The primary approach of biofilm formation is the creation of a stable and homeostatic environment that enhances the growth, cell-population density, and also provides bacterial resistance and protection. When the biofilms are adhering to plants, humans, or non-living surfaces, they can form a symbiotic relation, but pathogens bacteria can leave their native niche and adhere to other tissues producing adverse effects.

There is an important relationship between the colonized surface and the formation of the biofilm, this adherence is mediated by different types of interactions, from environmental factors, physicochemical interactions, and characteristics of the material. In the case of fibers, which are polymers, they have emerged to act together with some materials or alone to create new biomaterials for clinical purposes. When biofilms colonize those materials, it represents a danger to human health, since the defense barriers are altered, facilitating the transmission of pathogens, and leads to bacteremia or serious infections, commonly known as nosocomial diseases/infections or health care-associated infection, that is they are infections acquired in the hospitable environment.

For 2012, the International Nosocomial Infection Control Consortium (INICC) investigates that the mortality rate associated with nosocomial diseases in Ecuador can reach 38%. Given this and the impact that biomaterial-associated infections have on public health systems, it is important to determine the mechanism by which biofilm is formed. Hence, this thesis provides an overview of bacterial adhesion, as well as the material properties, the risk associated infections (pathogenesis) that it implies in a public health context. Finally, the applications and approaches of fibers are reviewed, mostly associated for their uses in the biomedical field.

Keywords: biofilm, bacterial adhesion, pathogenesis, infection, fibers

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1. INTRODUCTION

Biofilm is a living form of most of the bacteria, which relies on a beneficial relationship. Its system is called a biofilm and it provides growth, stability, and durability on time to the bacteria, due to the protective symbiosis their structure confers (Donlan, 2002; Khatoon et al., 2018; Li Xu & Siedlecki, 2020). However, it can be pathogenic for humans leading to chronic infections, especially when the infection is derivate from an implant or biomaterial associated infection (Donlan, 2002; Paul Stoodley et al., 2013). This review highlights the dynamic of biofilm formation, the interaction on the common biomaterial surfaces, in addition to pathogenesis that it implies in a public health context, and finally, the applications of fibers in the biomedical field, to provide future approaches of investigation of them.

2. MOTIVATION

2.1. Problem statement

The infection associated with biomaterials, whether implantable or non-implantable materials, leads to one type of infection, surgical site infection (SSI). SSI is a type of nosocomial disease or health care-associated infection (García, 2016; Tite, 2013; Vásconez et al., 2019) and occurs within 30 days of the surgical process or one year after an implant has been placed (Ministerio de Salud Pública, 2006). According to the Centers for Disease Control and Prevention (CDC), there are three types of SSIs, (1) superficial incisional infection (affecting skin and skin cell tissue), (2) deep incisional infection (affecting deep soft tissue), and (3) organ-space infection (involving organs other than the incision) (Vásconez et al., 2019).

In Ecuador, according to the Ministry of Public Health (MSP) (2016) superficial incisional infection represents 60-80% of wound infections. Quantitatively, the MSP mentions that by taking samples of the affected tissue and if it exceeds 100,000 bacterial colonies per gram of tissue, the SSI is confirmed (Ministerio de Salud Pública, 2016). Meanwhile according to a study conducted by INICC, nosocomial diseases have an associated mortality rate ranging from 14% to 38% (Rosenthal et al., 2012). Additionally, the cost of care for a

patient with a nosocomial infection is 4 times higher than expected for patients with similar diseases but without a nosocomial infection (Ministerio de Salud Pública, 2006).

Table 1. Surgical site infections and possible pathogens (Alemán & Miño, n.d.).

Surgical Site Infection	**Pathogen**
Placement of graft, implants, prostheses. Cardiac. Neurosurgery. Breast. Orthopedic (hip replacement, trauma, closed fractures, prosthetic material). Vascular. Non-cardiac thoracic.	*S. aureus, Coagulase negative staphylococcus*
Ophthalmic	*S. aureus, Streptococci, Coagulase negative staphylococcus*
Thoracic (lobectomy, pneumonectomy)	*S. pneumoniae, Gram-negative bacilli*
Appendectomy. Biliary tract.	*Gram-negative bacilli, anaerobios*
Obstetric and gynecological.	*Gram-negative bacilli, Enterococcus, Streptococci*
Urological	*Gram-negative bacilli*

Biofilms in the field of medicine lead to bacterial contamination at the tissue-material interface, and in turn contribute to: chronic infections, increased antimicrobial resistance, implant removal, and in the worst case, patient death. These factors, have caused a greater degree of research attention to be directed towards the development of microbe resistant materials/surfaces, several studies use natural polymers for their manufacture, as natural and synthetic fibers since they can prevent initial bacterial adhesion and eventually the formation of biofilms.

Ecuador is a “megadiverse country”, due to its vegetation, as a result companies export fibers to all over the world to be manufactured, especially in the textile industry (Asociación de Industriales Textiles del Ecuador, n.d.; Cobos, 2017). In Ecuador, it is

possible to use natural sources for the study of fibers with antimicrobial properties, because they can prevent the formation of biofilms (Alexis & Romero, 2019). Then with the extraction of these natural resources and its subsequent manufacturing, the respective analyses of chemical, physical, mechanical and topography properties could be performed to provide new strategies for the uses of the fiber to reinforce biomaterials for the biomedical field.

2.2. Objectives

General objective:

- To describe the biofilm formation and its interaction with biomaterials.

Specific objectives:

- To explain the mechanisms of biofilm formation.
- To expose the biomaterial surfaces properties and its interaction with bacteria.
- To elucidate the different approaches of the fibers in the biomedical field.
- To describes the importance of Ecuadorian native fibers.
- To describe the biofilm formation in natural fibers

3. THEORETICAL FRAMEWORK

3.1. BACTERIAL ADHESION AND DYNAMICS OF BIOFILM FORMATION

Bacteria are widespread everywhere around us, in air, water, food, soil, and in all living bodies (Hamasha, 2011), and of that they have developed adaptive mechanisms referring to controlling gene expression to both maintain essential functions and modulate accessory functions in response to environmental cues (Lejars & Hajnsdorf, 2020). These traits have made bacteria an ideal microorganism for living in Earth during approximately 3.8 billion years ago (Cooper, 2000) Bacteria living forms occur naturally in the environment, as planktonic and biofilm, the first type exist freely and the last as a unit attached to any surface that accomplish with certain properties (charge, hydrophobicity, roughness and so on) that can mediate initial bacterium attachment (Garrett et al., 2008; Zambrano & Suárez Londoño, 2006).

Due to their cell wall envelope, bacteria react differently when stained with the Gram stain (crystal violet and an iodinated solution), classifying them into Gram-positive and Gram-negative bacteria with a purple brown and red/pink stained color under microscopic, respectively. Gram-positive bacteria possess a thick (20–80nm) cell wall as the outer shell of the cell. Otherwise, Gram-negative bacteria have a thin (<10nm) layer of the cell wall but harbor an additional outer membrane with several pores and appendices. These morphological differences in the cell wall envelope confer different properties to the cell, in particular, responses to external stresses, including heat, UV radiation, and antibiotics (Mai-Prochnow et al., 2016).

Moreover, Gram-positive have a larger fraction of negatively charged phosphatidylglycerol (Malanovic & Lohner, 2016), they are primarily cationic in nature compared with Gram-negative bacteria (Garrett et al., 2008; Laverty et al., 2015). For example, in Gram-positive *Staphylococcus aureus* the presence of teichoic acids, highly negative-charged cell wall polymers because of presence of phosphate in their structure, help to the binding to plastic surfaces (Reffuveille et al., 2017; Tofail, 2011). The description of the major structural differences between gram positive and negative bacteria is given in Table 2.

3.1.1. The structure of microbial biofilms

In general, the biofilm can be described as a tightly packed of bacteria cells with water channels (Brindhadevi et al., 2020). Then, the mechanism of biofilm formation developed by the bacteria depends on the organism type (bacterium strain), the environment conditions (including nutrients), and the adhering surfaces (Cegelski et al., 2019; Zambrano & Suárez Londoño, 2006).

According to Laverty et. al., (2015) the general biofilm process involves 3 stages: *adherence, accumulation, and dispersal*. Figure 1 shows the biofilm process. The adherence step involves translocation to the surface substratum with reversible and irreversible adhesion. Once the bacterium attaches to the substrate the accumulation step is driven by the molecular mechanisms triggered by the bacterium, in which some genes are expressed in response to fluctuations in cell-population density, known as quorum sensing (Miller & Bassler, 2001). The presence of a matrix characterizes this phase of bacterial growth, mainly composed of extracellular polymeric substances (EPSs), such as polysaccharides, proteins, fatty acids, and extracellular DNA (eDNA) (Ramirez-Mora et al., 2019), which along with the surfaces have provided the protective conditions for the attached cells to potentially create a localized homeostatic environment (P. Stoodley et al., 2002). The final stage includes the dispersion of planktonic cells (single cells), which is a transition from the mature biofilm to other surfaces for recolonization.

3.1.2. Adherence of biofilm

Both Gram-negative and Gram-positive bacteria present some interactions that mediate the initial reversible-binding at the contact surfaces, such as hydrophobic and ionic interactions (Laverty et al., 2015). The forces and bond formations reported involve hydrogen bonds, London forces, Van der Waal interactions, non-covalent forces acting at large separation distances of >50nm and electrostatic interactions acting at distance of 10–20 nm (Benčina et al., 2018; Cegelski et al., 2019).

Under physiological conditions, bacteria prefer to adhere to chemically-positive charged surfaces, due to cell wall and cell membrane components that present negatively charged phosphate groups, carboxyls, and other acidic groups. Additionally, the surface-exposed proteins also provide a negative net surface charge from most bacterium (Cegelski et al.,

2019). On the one hand, Gram-negative bacteria tend to be neutral or polyanionic due to the presence of ketal-linked pyruvates or uronic acids (anionic properties), which allows the association of calcium and magnesium, these divalent cations increase the binding force to the surface in the bacterial community (Vu et al., 2009).

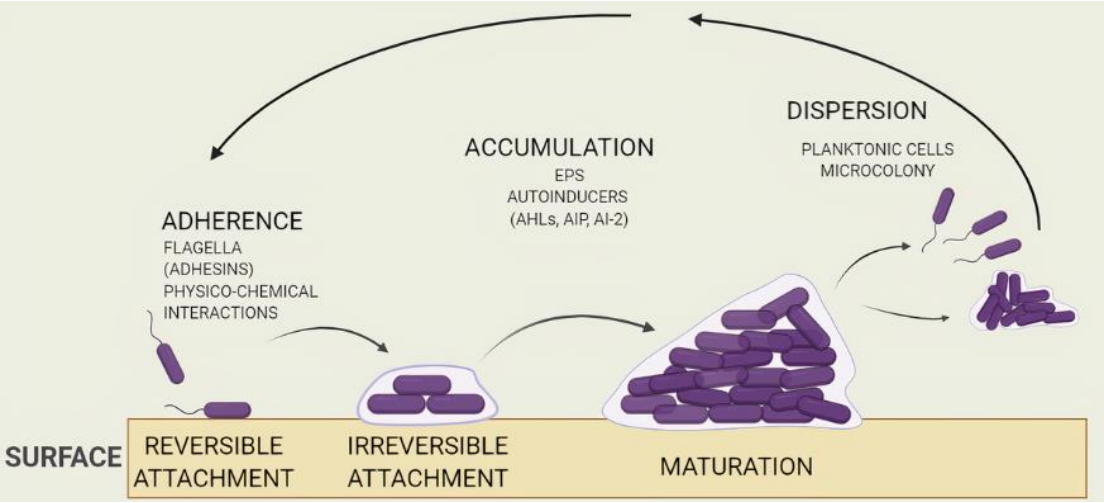

Figure 1. The composition and formation stages of a model biofilm

Furthermore, specific interactions are related to molecular components of the cell wall, known as adhesins. The adhesins are bacterial molecules present on their surfaces that mediate specific binding to a receptor on a target cell (Cegelski et al., 2019). That is helping to acquire a permanent adhesion regardless the environmental conditions (Berne et al., 2015).

There are two types of adhesion that include, fimbriales and afimbrial adhesins. The first type are proteinaceous filamentous projections on the bacterial cell surfaces found in virtually all Gram-negative bacteria but not in many Gram-positive bacteria, they are important in adhesion to host surfaces. (Berne et al., 2015; Salton & Kim, 1996); while, the second type has a composition of proteins and lipoteichoic acids from the external membranes. (Cárdenas et al., 2014). For instance, *Escherichia coli* can often express multiple adhesins during infection to favor attachment to the urinary tract (Berne et al., 2015; Snyder et al., 2005), The responsible for this aim is the type 1 pilus, it is composed of 500–3000 copies of FimA gene resulting in a fiber that is 1 to 2 μm long and 6.9 nm wide and is a phase-variable virulence factor (VF) highly expressed adhesin involved in early

colonization and urinary tract pathogenesis. At the end of the type I pilus it has a tip adhesin FimH, when it is absent reduces adherence and biofilm formation (Berne et al., 2015; Sanderson et al., n.d.; Snyder et al., 2005).

Similarly, the Gram-positive also produce adhesive pili, which are formed by covalent polymerization of pilin subunits (Cegelski et al., 2019). For example, Pilus Island 1 (PI-1) is a group of genes belonging to B Streptococcus (GBS) pilin subunit, which is responsible for facilitating adhesion and invasion of host cells from, *Streptococcus pyogenes* and *Streptococcus pneumoniae* (S. Jiang et al., 2012).

Another important structure in Gram-positive bacteria is the presence of lipoproteins, which usually comprise molecules that are non-surface exposed but located between the cytoplasmic membrane and the peptidoglycan (PGN), equivalent to the periplasm of Gram-negative. A few of these lipoproteins have been identified by their ability to act as adhesins, allowing these organisms to adhere to a variety of substrates (Fischetti, 2016). For example, SsaB is a lipoprotein from *Streptococcus sanguis* that shares sequence homology with other streptococcal adhesins and has been implicated in the interaction with human salivary receptor and coaggregation with *Actinomyces naeslundii*. The poor buccal hygene can contribute to biofilm formation, then into caries pathogenesis and in worse situation can lead to ineffective endocarditis disease (Crump et al., 2014; Lockhart et al., 2009; Zhu et al., 2018).

Table 2. **Differences between Gram-positive and Gram-negative bacteria structures (Malanovic & Lohner, 2016; Salton & Kim, 1996).**

Gram-positive	Gram-negative
Cytoplasmic membrane surrounded by a cell wall (periplasmatic space)	No cytoplasmic membrane. The periplasm occupies the space between the inner membrane and the outer membrane.
LTA in the cell wall	LPS in the outer membrane
The cell wall is made of many PGN layers of about 40–80 nm.	The cell wall is made of many PGN layers of about 7–8 nm.
Primarly cationic (in nature compared with GN)	Tend to be neutral or polyanionic (ketal-linked pyruvates or uronic acids)
Lipoproteins acts as adhesins	Pili mainly mediate the adhesion

Abbreviations: lipoteichoic acid (LTA), lipopolysaccharide (LPS), peptidoglycan (PGN), Gram-negative (GN).

3.1.3. Accumulation and dispersion of biofilm

As previously mentioned, there is a specific relation between the cells and the biofilm formation, which is usually mediated by the cell aggregation of the same bacteria strain mediated by communication among the bacteria. It corresponds to the *quorum sensing* (QS) mainly mediated by genes that are activated in the response of bacteria cell density to regulate the metabolic and behavioral activities of a bacterial community (Brindhadevi et al., 2020; J. Huang et al., 2019; Vadakkan et al., 2018).

Most of Gram-positive and Gram-negative bacteria coordinate physiological responses, by QS signal circuits (Lade et al., 2014). Studies report the importance of the Acyl Homoserine Lactones (AHLs), which are small diffusible molecules with a core lactone ring and an acyl side chain (Vadakkan et al., 2018). The AHLs represent to the autoinducer (AI) responsible for facilitating signaling in Gram-negative bacteria (Lade et al., 2014; Papenfort & Bassler, 2017; Parsek & Greenberg, 2000). Meanwhile, Gram-positive synthesize Autoinducing Peptides (AIP). Finally, Gram-negative and positive bacteria produce AI-2 signals (Q. Jiang et al., 2019). The processes controlled by QS include bioluminescence, sporulation, competence, antibiotic production, biofilm formation, and virulence factor secretion, those processes are essential for the survival of biofilm and evasion from harsh dynamic environmental conditions. (Brindhadevi et al., 2020; Garrett et al., 2008; Y. H. Li & Tian, 2012; Rutherford & Bassler, 2012).

In Gram-negative bacteria, as soon as the AHLs accumulate in the extracellular environment and exceed the threshold level stablished by experimental data calculation of the rates of autoinducer synthesis over time and varying from different bacteria cultures. (Scholz & Greenberg, 2017). AHLs signal molecules will diffuse across the cell membrane, and then bind to specific QS transcriptional regulators, thereby promoting target gene expression (Q. Jiang et al., 2019). Similarly, the signal molecules AIPs which are synthesized in Gram-positive bacteria -when the cell density is high- they are secreted by membrane transporters by diffusion to modulate the transcription factor's activity and, in turn, modulate gene expression changes (Ng & Bassier, 2015; Rutherford & Bassler, 2012; Vadakkan et al., 2018).

The accumulation stage involves the maturation of biofilm and subsequently the EPS production (Khatoon et al., 2018). The composition of biofilm consist of about 80% EPS and its production is influenced by the conditions of the environment (Nazar, 2007), which include different levels of oxygen and nitrogen, the extent of dryness, temperature, pH, and availability of nutrients (e.g. phosphorous) (Vu et al., 2009).

The secretion of EPS that involve a mixture of water channels and polysaccharides proteins (composed primarily of D-amino acids), lipids, lipopolysaccharides, and a variety of nucleic acids. EPS is a matrix mostly composed of water channels, that facilitates adhesion between bacteria and surface (Khatoon et al., 2018). There is an important relation between the QS and the production of EPS which allows the biofilm to switch responses, from a colonization mode (with an optimized growth rate) to a protection mode (Frederick et al., 2011; J. Huang et al., 2019).

For example, in *Pseudomonas aeruginosa*, the biofilm formation is mediated by the Rhl QS system (Table 3), by regulating the glycolipid biosurfactant rhamnolipid. The glycolipid acts during the formation of biofilm, maintaining the channels for the fluid of nutrients and in the motility of planktonic cells (Brindhadevi et al., 2020). Moreover, a recent study suggested that lectin *lecB* gene stabilizes the biofilm matrix when it is bound to Psl exopolysaccharide, and it is quorum sensing controlled (Passos da Silva et al., 2019). Table 3 shows a list of autoinducers reported in Gram-positive and Gram-negative bacteria.

In another work looking into the autoinducers, Xu and colleagues (2006) used *Staphylococcus epidermis*, to demonstrate the functionality of *luxS* autoinducer, during the biofilm formation. These authors worked with an *luxS* mutant strain, and the wild type bacteria, and assays using microtiter plates. The results showed that the mutant strain significantly ($P < 0.0001$, two-tailed t-test) increased biomass (1.7 times) compared to the wild-type strain, it was also confirmed by the scanning electron microscope characterization (SEM). The increase of biomass of the mutant strain was accompanied by a more compact and thicker biofilm, which have a greater significance in the biofilm development and virulence of *S. epidermis* and subsequently in the biofilm-associated infection govern by the luxS QS system. Also it represents a general scheme of other acting mode staphylococci.

Table 3. Autoinducers participant in the formation of biofilm of common Gram-positive and Gram-negative bacteria strains.

Bacteria strain	Molecular Auto-inducer	QS signaling molecule	Reference
Gram-Negative			
Pseudomonas aeruginosa	RhlI	Acyl Homoserine Lactone	(Brindhadevi et al., 2020)
Escherichia coli	CsrA		(Constanza Muñoz et al., 2017)
Vibrio cholerae	CytR		(Haugo & Watnick, 2008)
Vibrio fischeri	LuxI		(Miyashiro et al., 2014; Ng & Bassier, 2015)
Gram-Positive			
Staphylococcus aureus	SarA	Autoinducing Peptides	(Balamurugan et al., 2017)
Staphylococcus epidermis	LuxS		(Lin Xu et al., 2006)
Streptococcus mutans	LuxS/ComCDE	AI-2	(Cvitkovitch et al., 2003; Y. H. Li & Tian, 2012)
Streptococcus pneumoniae	LuxS		(Cvitkovitch et al., 2003)

3.2. BIOMATERIAL-BACTERIUM INTERACTION

3.2.1. Surfaces properties of biomaterials

A biomaterial is a substance engineered to act alone or in conjunction with a complex system, and capable of interacting with living organisms, in order to fulfill a treatment or diagnostic procedure (e.g.: dental implants, intraocular lenses, pacemakers, biosensors) (Hudecki et al., 2019). Given the use of biomaterials in the health field, microbial adhesion and the subsequent formation of biofilms, occur frequently in many medical applications (Katsikogianni & Missirlis, 2010), which eventually leads to severe complications associated with the use of biomaterials, better known as biomaterial-associated infection.(Li Xu & Siedlecki, 2020).

The attachment of bacteria to any surface depends not only on the molecular mediation of bacteria but is also greatly influenced by the properties of the material surface. In general, the rule is that bacterium prefers hydrophobic and roughness surfaces, instead of hydrophilic and smooth surface (Donlan, 2002; Nazar, 2007; Renner & Weibel, 2011). It is because bacteria are generally hydrophilic and the displacement of water molecules near surfaces enhances hydrophobic interactions, while surfaces roughness provides more surface area for the bacterium-cell adhesion (Renner & Weibel, 2011). However, this is not always the case. In this section, will be discussed how the physicochemical, topographical and mechanical properties of materials could affect the bacterial adhesion and consequently the biofilm formation (Araújo et al., 2019; Reffuveille et al., 2017; Renner & Weibel, 2011).

3.2.1.1. Physicochemical properties of biomaterials

Physicochemical properties involve: electrostatic interactions and surface energy (Almaguer-Flores, 2013). Initially, the studies about bacterial adhesion was stablished by Derjaguin, Landau, Verwey, and Overbeek, well-known theory DLVO, which is based on thermodynamic studies on the calculation of Gibbs free energy of a given system (e.g. liquid-solid, bacteria-liquid, and bacteria-solid interfaces). The theory assumes that microbial cells acts as colloidal particle and along with the substratum, they behave as inert particles (Bayoudh et al., 2009; Li Xu & Siedlecki, 2020). The interactions are based on

Lifshitz-van der Waals (LW) attractive forces and double-layer electrostatic (EL) interactions, adopting that they are independent and that they overlap or add at each interaction distance for two particles (Acuña & Toledo, 2010; Mechanisms, 2001). When the Gibbs free energy value is negative, result in the adhesion of bacterium with the surface (Garrett et al., 2008; Renner & Weibel, 2011; Li Xu & Siedlecki, 2020).

An updated version of this theory is extended DLVO theory (XDLVO) (Bayoudh et al., 2009), which not only taking into account the LW and EL but also the Lewis acid-base interactions, which leads to the formation of covalent bonds between the cell and surface (Cheng et al., 2019).

Both theories are classic concept of colloid behavior that characterizes a planktonic bacterial cell as a smooth particle that interacts with a surface in a manner based on the charges on both surfaces, which overcome the basic repulsion of individual particles (Paul Stoodley et al., 2013). It means that, due to is well-know that bacterial cell envelope provides net negative charge (as measured by zeta potential; often determined by estimating the electrophoretic mobility of bacteria cells) (Wilson et al., 2001), bacteria are subjected to repulsive electrostatic forces when approaching to surfaces with similar electrostatic charges while bacteria are highly adhesive or bound to positively charged surfaces (Berne et al., 2015). Table 4 provides information on surface properties and bacterial response.

Table 4. Ssurface properties of different materials and bacterium response.

Material	**Surface features**	**Bacterium response**	**Reference**
Silicon	Using silicone negative moulds of cicada wings with Poly (methyl methacrylate) PMMA films.	Efficacy in preventing *E. coli* adhesion.	(Linklater et al., 2017)**.**
	Black silicone. Nanograss, diameter 20–80 nm, height 500 nm.	Antibacterial activity against *P. aeruginosa* , *S. aureus* and *B. subtilis*	**(**Tripathy, 2017**)**

Table 4. Continued.

Material	Surface features	Bacterium response	Reference
Polysty-rene	Pillar structure, diameter of pillar 1.85 μm, period 5 μm (note: these are micro- not nano-structures).	Enhanced *S. aureus* adhesion.	**(**Tripathy, 2017**)**
PEEK	Micro/nano-topographic PEEK with specific functional groups (amino and COOH/COOR). Sulfonation and argon plasma modification, causing the electrostatic repulsion between the surfaces and negative bacteria.	Preventing adhesion of *E. coli* and *S. aureus*.	(S. Wang et al., 2018)
Zirconium	ZrN-coated titanium samples, with Ra value of 0.28 μm.	Reduced the adhesion of *S. mutans, S. gordonii, and S. intermedius*	(Franková et al., 2013)
Titanium	Nanopatterned arrays, average diameter 40.3 nm.	Effective in killing *P. aeruginosa* , and less lethal against *S. aureus*	**(**Tripathy, 2017**)**
	Ti-GO-Ag nanocomposite (GO film, increase elastic modulus and Ag nanoparticles, increase surface area and decrease hydrophilicity of surface).	Effective in inhibing *S. aureus* division and effective in destroying was against *E. coli* by the integrity of bacterial cell wall.	(Jin et al., 2019)

Table 4. Continued.

Material	Surface features	Bacterium response	Reference
Titanium	Ti6Al4V modified with nano-texturing and silver nano-particles.	Antibacterial effect against *S. epidermidis, S. aureus, E. faecalis, E. coli* .	(Gallo et al., 2019)
Stainless steel	Modification by duplex plasma silvering–nitriding technique. Ag agents and a wear-resistant S-phase have been generated on stainless steel.	Bactericidal activity against *E. coli* and *S. epidermidis*	(Dong et al., 2011)
Chitosan	Chitosan-based films with incorporated supercritical CO_2-HE, showed a tensile strength (from 14.4 MPa to 6.4 MPa) and Young's modulus (from 218.8 MPa to 26.9 MPa).	Antibacterial activity against *B. subtilis.*	(Baji et al., 2019)

Abbreviations: titanium (Ti), graphene oxide (GO), silver (Ag), polyetheretherketone (PEEK), alpha-beta titanium alloy (Ti6Al4V), superhard expanded austenite phase (S-phase), carbon dioxide (CO_2), hop extract (HE).

Thus according XDLVO and DLVO the tendency of as zeta potential becomes less negative, electrostatic repulsion decreases, and so does bacterial adhesion, driven by van der Waals interactions, it cannot be extrapolated to all bacteria-surfaces interaction (Wilson et al., 2001), because there are properties such as shear generated by local hemodynamics (Katsikogianni & Missirlis, 2010) that can contribute to the bacterial adhesion (Bayoudh et al., 2009).

Hydrophobicity can be defined as low surface energy and electrostatic charged surface, which increases the bacterial adhesion in most cases (Reffuveille et al., 2017). According to Xu et al. (2020), bacterial adhesion was most remarkable on hydrophilic substrates with positive surface charge characteristics, followed by hydrophobic substrates with negative surface charge characteristics, with the smallest bacterial adhesion on hydrophilic substrates with negative surface charge characteristics (Li Xu & Siedlecki, 2020). This preferential pattern was reported in a study using *S. epidermidis* adhesion on the alkyl silanized glass surfaces. The results showed that the CH_3 terminated surface produced the highest adhesion, followed by the positively charged NH_2 functionalized surface, the non-charged NH_2 groups, the COOH, and minimal adhesion was observed on the OH-terminated glass surface (Katsikogianni & Missirlis, 2010). These results suggested that the increase in the material surface's free energy reduced the adhesion of *S. epidermidis* strain, which follows the predictions by the thermodynamic XDLVO theory (Li Xu & Siedlecki, 2020).

In terms of bacterial-biomaterial surface interaction, the hydrophobicity is also given by the bacteria surfaces properties (Song et al., 2015), which include cell surface structures such as fimbriae, proteins, LPS, EPSs, and flagella (Donlan, 2002). For instance, bacteria fimbriae mediate cell surface bonding, overcoming electrostatic repulsion with the substrate (Donlan, 2002). Specifically, in staphylococci, the polysaccharide intercellular adhesion (PIA), an adhesive biofilm molecule, provides a positive charge in the negatively bacterial cell surface environment, resulting in a more bacterial adhesion in surfaces. Furthermore, PIA acts as glue by sticking the cells together via electrostatic interaction between bacterium and substrate (Formosa-Dague et al., 2016; Reffuveille et al., 2017).

In addition, in a study by Beaussart et al., (2018), focused on probing the influence of cell surface polysaccharides on nanodendrimer binding to both Gram-positive and Gram-negative bacteria. The authors employed 4 bacteria strains, 2 mutant and 2 wild type bacteria, represented by *L. lactis PSP* (lacking their native surface polysaccharide pellicle), *E. coli LPS* (which express surface O-antigen at their surface), *L. lactis WT* and *E. coli WT*, respectively. To observe whether repulsion or attraction between bacteria and nanodendrimer surface and atomic force microscope (AFM) equipped with a tip covalently

grafted with PAMAM nanoparticles (NPs), and create a virtual mesh (32 x 32 pixels) in order to sense long-range electrostatic interactions between the dendrimer and the bacterial surface. It was found that binding to the cell surface is predominantly driven by electrostatic interactions and that NP adhesion features are strongly mediated by both the polymeric biomolecules carried by the bacteria and the composition of the supporting cell wall structure (Beaussart et al., 2018).

3.2.1.2. Topographical and mechanical properties

Surface roughness is considered an important factor for concerning bacterial adhesion. At first, it was determined that surfaces with physical imperfections such as pores, cracks, i.e., those who have colossal roughness, are a better prospectus for the adhesion of biofilms. This is due to the shear forces (forces on the surface) that are diminished, the higher surface area, additional adhesions sites and protective environment present in such as surfaces (Benčina et al., 2018; Boyd et al., 2002; Donlan, 2002).

The methods for characterizing roughness are performed with surface roughness testers, whose functional principle is based on a scanning cantilever in contact with the substrate to obtain the Ra and Rz roughness parameters of the substrate. Hence, the Rz is the the average depth of roughnes and Ra parameter corresponding to the arithmetic mean of the absolute amounts of all variances in the roughness profile from the centre line in the total measured material distance (Amaral et al., 2009). The roughness of the material will depend on its natural conformation or also on the handling of the materials by chemical physical methods, such as modification of polymer surfaces or by means of surface mechanical abrasion treatment, respectively (Encinas et al., 2012; Mincheva et al., 2017).

In general, the pristine surfaces, such as stainless steel, titanium, has been reported to be less favorable for bacterial adhesion (Benčina et al., 2018; Taubert et al., 2013). In this context, surfaces with arithmetic mean roughness (Ra) value of $\leq 0.8\mu m$ are typically considered "hygienic," whereas those with a $Ra > 0.8\mu m$ are more susceptible to bacterial deposition (Hsu et al., 2013). Nevertheless, stainless steel and titanium orthopedic screws, allows the binding for *P. aeruginosa, S. aureus,* and *S. epidermidis* (Benčina et al., 2018), in fact in orthopedic surgery, the reported infection rate is more in stainless steel when compared to titanium alloys as the latter favor easy formation of soft tissue (Veerachamy et

al., 2014). It is due to stainless steel is a material with a high surface energy which are mainly hydrophilic and frequently negatively charged, then susceptible to contamination (Ho et al., 2014). Moreover, it has been also revealed that the micro and nano surface properties of the materials (which are presented in figure 2) would influence the bacterial adhesion differently than the bulk material (Arango-Santander et al., 2018; Cheng et al., 2019; Ferraris et al., 2019).

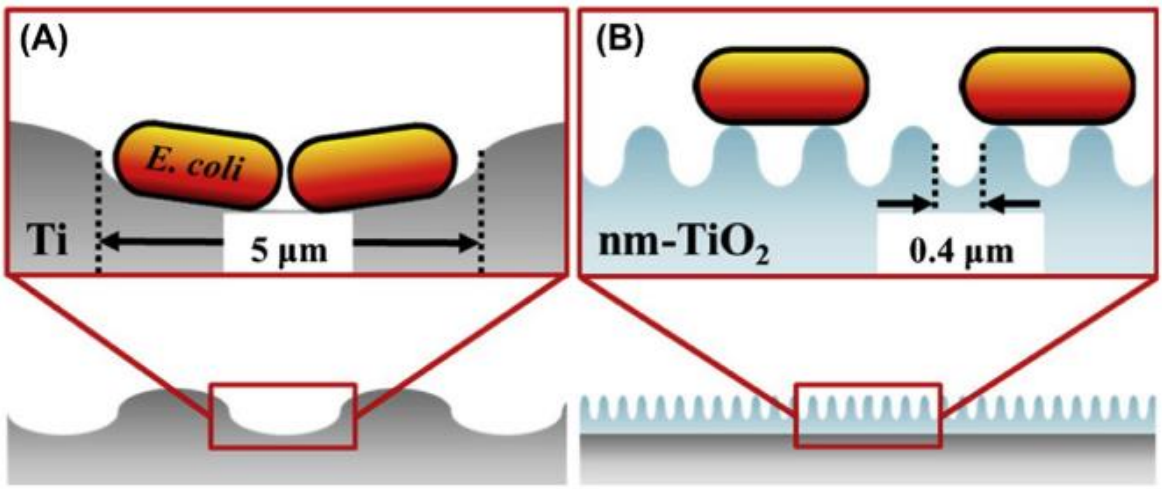

Figure 2. The comparison of bacterial spatial configuration on surfaces with micro (A) and nanostructured (B) topography (Benčina et al., 2018)

Studies report that high roughness on surfaces promotes bacterial establishment due to mechanical retention in micro surfaces, as well as they provide high surface attachment and protection from shear forces to cells. Furthermore, nano roughness (sizes 100 nm) improves the capacity of surfaces to avoid bacterial adhesion (Hsu et al., 2013; Taubert et al., 2013). It was confirmed in a study conducted by Boyd et al. (2013) they used *S. aureus* bacteria to study the preference of biofilm formation to stainless steel with different roughness topographies. The studies reported better bacterial adhesion to rough stainless steel compared to smooth surfaces. There was a maximum area of contact of the cell and the surface, when the surfaces had the same scale of 1 *µm* as *S. aureus* (Hsu et al., 2013).

However, a rough surface is not always more preferred by bacterium. This was demonstrated by Park and colleagues (2008), they design an experimental system chamber under three different nutrient conditions to evaluate the metabolism rate and continuous

bacterial attachment onto nanophase titania (NT) and nanometer-smooth topography (NST) materials. Authors focused on measuring light emission of *Pseudomonas fluorescens* and *Pseudomonas putida* (bioluminescent bacteria) attached NT and NMT surfaces. Taking account that the bacteria bioluminescence increase while the bacteria population increase, the results showed greater bioluminescence rates per cell in the surface of the NT, which means, stronger adhesion on NT than in the NST surface (Park et al., 2008).

Similarly, the surface roughness was evaluated by the bacterial adhesion and subsequently biofilm formation of *Pseudomonas aeruginosa* on three different surfaces, untreated Ti, plasma nitriding, and plasma carbonitriding Ti substrates (Nunes et al., 2018). An inverse correlation between bacterial adhesion and the surface roughness was revealed for the plasma carbonitriding Ti (TiCN) sample, which was rougher exhibited less adherent to *Pseudomonas aeruginosa*$^{-}$, than the (untreated) Ti sample (low wettability and smooth surface) However, in this study surface roughness was not a determinant factor for controlling bacterial adhesion due to TiN has the second higher contact angle showed the maximal performance against bacterial adhesion (Nunes et al., 2018). Instead, the chemical composition of the surface due to valence of Ti on the surface, because the nitriding mechanism, produces TiN with trivalent Ti cations, seems to have a beneficial action to improve the performance of the surface to retard bacterial adhesion (Nunes et al., 2018).

Furthermore, it is important to mention the effects that the topography has at the individual cellular level also affects multicellular clusters and biofilms. The parameters such as interstitial space, the surface, and the depth are determining whether or not aggregation of bacterial cells occur. In this regard Lai (2018) have reported that in the Si nanogratings the number of bacterial cells was reduced by 20% compared to those of the control (surface without nanogratings), it was because the physical trapping of bacteria at the bottom (depthness >50nm) of the nanogratings (Lai, 2018).

In another study, Yoda et al. (2014) evaluated the ability of *Staphylococcus epidermidis* to adhere to the surface of solid biomaterials at different levels of roughness below 30 nm Ra. The authors investigated the minimum level of roughness required to promote bacterial adhesion (during 60 minutes without biofilm formation) on five types of biomaterials: oxidized zirconium-niobium alloy (Oxinium), cobalt-chromium-molybdenum alloy (Co-Cr-

Mo), titanium alloy (Ti-6Al-4 V), commercially pure titanium (Cp-Ti) and stainless steel (SUS316L). These samples were categorized into a fine group and a coarse group according to surface roughness. The surfaces specimens were physically analyzed and the viable bacterial density of the adhered bacteria was quantitatively determined. The results from this study showed that even quite a low surface roughness range of 8.5-30.0 nm Ra for Oxinium, 7.1-16.5 nm Ra for Ti-6Al-4 V and 1.8- 7.2 nm Ra for SUS316L can influence initial bacterial adhesion.

Similarly, Hsu et al. (2013) studied the effect of topography on the adhesion of various bacterial cells (*Escherichia coli, Listeria innocua, and Pseudomonas fluorescens*) to silica and alumina surfaces. The authors used nanosmooth surfaces and also the substrates were engineered to create patterns of pores in both materials (Hsu et al., 2013). The results indicated that the bacteria appeared to attach equally onto the nanoporous alumina membranes, whiles there was a trend for the bacterial attachment to the nanosmooth alumina and the silica substrates (Ra of 4.9 nm^a and 0.3 nm^a respectively). Then, the results suggest that *E. coli (*ATCC25922) and *L. innocua* had more attachment on the nanosmooth (control) and *E. coli* (O157:H17) and *P. fluorescens* had attachment to the nanoporous substrate (Hsu et al., 2013). This findings suggest that bacteria can maximize contact area and surfaces, while alignment cells depending on the topographical such as dimension of porous and roughness surfaces (Hsu et al., 2013).

It is noteworthy that, there is no a trend for the topography of materials, because there are also other variants that must to be considered. Particularly, knowing topography can also induce changes in the physicochemical properties on surfaces respect to bacteria, as well as differences in pore size (Cheng et al., 2019).

Another important aspect to consider is that the survival of bacterial cells depends on the capacity of a living organism to response to environmental pressures including a range of mechanical forces such as the response of the living cells to the mechanical forces from the environment has critical effects on their ability to grow, differentiate, survive, and ultimately adhere to surfaces (Araújo et al., 2019).

The important mechanical properties are rheological properties and viscoelastic properties, which could be determined by applying forces and measuring displacements (of samples:

material or bacteria biofilm) as functions of the imposed load (Araújo et al., 2019). This procedure, known as active micromechanical measurements, which can be used for determining the material's Young's modulus (e.g. elasticity) and for determining the stiffness, shear stress of the bacteria by analyzing the sample deformation in response to an imposed stress (Araújo et al., 2019; Boudarel et al., 2018; Karampatzakis et al., 2017).

The mechanical parameters for the biofilm are given by the matrix of EPSs, that holds the cells together providing the mechanical stability of the biofilm (Karampatzakis et al., 2017). Some of EPSs are alginate, xanthan, and gellan gum, which are aggregated due to hydrogen bonding to form highly hydrated viscoelastic gels (Garrett et al., 2008; Subramanian et al., 2020).

The EPSs provides irreversible viscous deformation and reversible elastic response and recoil of biofilm at its different stages of development. (Araújo et al., 2019; Garrett et al., 2008). For example, the Psl exopolysaccharide in *Pseudomonas aeruginosa* biofilms, contributes to the stiffening of the matrix, as biofilms colonies grow, the localisation of Psl changes, leading to softening of the colony centres and the formation of hollow colonies (Boudarel et al., 2018; Karampatzakis et al., 2017).

Also this matrix responds to elastic tension, viscous damping, and alignment of polymers in the shear direction (Garrett et al., 2008; Subramanian et al., 2020), for example, the viscoelasticity of *P. aeruginosa* gives resistant to chemical treatment and strong shear forces, allow them to efficiently recover from mechanical damage (Araújo et al., 2019). In a study by Formosa et al., (2016), it was demonstrated that the adhesion of the staphylococcal surface protein and the mechanics of the material represent a general mechanism of pathogens to form the cellular aggregate and biofilm on the zinc-substrates (Formosa-Dague et al., 2016). Similarly, Castro et al. (2017) by studying the viscoelastic properties of *Staphylococcus epidermidis* and *Escherichia coli*, reported that there was a proportional relation between the shear modulus and the biofilm formation, due to as passing the different stages of the biofilm formation, the shear modulus values increase (Castro et al., 2017).

3.3. PATHOGENESIS AND RISK FACTORS ASSOCIATED WITH THE PRESENCE OF BIOFILMS ON BIOMATERIALS

The use of implants has represented an increase in the demands of biomaterials for biomedical purposes (Teo et al., 2016). In figure 3 are represented the most common biomedical applications of biomaterials. However, the number of infections related to their non-compatibility and pre-existing bacteria in the patient's body has also increased. (Paul Stoodley et al., 2013)**,** which has led to a loss of the implanted device. As mentioned previously, the formation of bacterial biofilms depends on the physicochemical, topographic and mechanical properties of the material's surfaces, as well as on the bacterial characteristics that determine the molecular conformation of the biofilm. However, other external factors such as the implant site, the extension or deepness of the implant colocation, the duration of the procedure and even the host microbiome, will influence in the development of biomaterial-associated infections (Rimondini et al., 2005). Thus, in development, the pathogenesis of bacteria when is in contact with biomaterials and the clinical consequences it represents is exemplified.

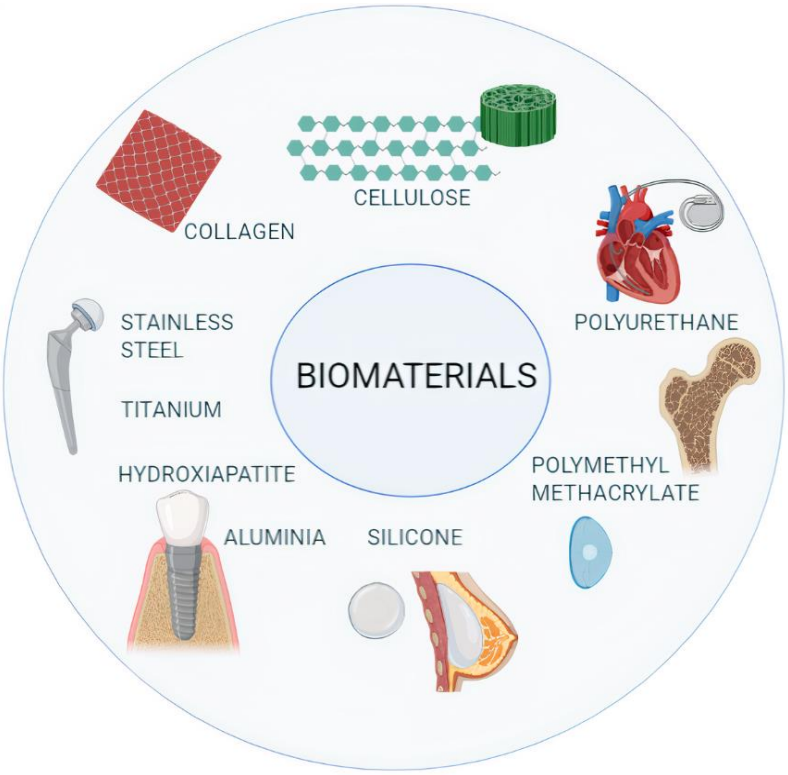

Figure 3. Common materials used in biomedical applications

3.3.1. Pathogenesis

Pathogenesis is the ability of an organism to produce damage or disease to the host. In the case of bacterial pathogenicity, it is mediated by virulence factors (VFs), which are molecules from or secreted by the bacterium that evokes disease in the host or vector (Peterson, 1996). These virulence factors are either secretory, membrane associated or cytosolic in nature. Also the pathogenic bacteria and non-pathogenic bacteria, secret small molecule or QS molecules that also stablish the infection (Sharma et al., 2017). Hence, the ability of bacteria to communicate and form biofilms through QS signals (e.g.: AHLs, AIPs, and AI-2) results in a virulence factor (see Table 3, page 18) (Vadakkan et al., 2018).

QS signals participate in the synthesis of VFs of Gram-positive and Gram-negative. In both cases, those VFs participate during bacterial growth and pathogenesis of the biofilm (Lade et al., 2014). For example, in Gram-negative *Pseudomonas aeruginosa* the factors synthetized by QS are pyocyanin and elastase, while in Gram-positive *Staphylococcus aureus* are fibronectin binding protein, hemolysin, protein A, lipase, and enterotoxin (Q. Jiang et al., 2019).

The most common human pathogenic bacteria include *S. aureus, Listeria monocytogenes, Enterococcus faecalis, Clostridium perfringens, P. aeruginosa, Serratia marcescens, Brucella melitensis* (Rutherford & Bassler, 2012). In order to explain the mechanisms of QS molecules that induce the synthesis of VFs, two representative and well-studied specimens of each bacteria gram stain will be elucidated: *V. cholerae* and *P. aeruginosa*.

S. aureus is a Gram-positive bacterium, which can lead to various infectious diseases such as bacteremia, infective endocarditis, osteoarticular, skin and soft tissue, pleuropulmonary, and device-related infections (Tong et al., 2015). In figure 4 is described the virulence control system of *S. aureus*. The bacterium employees a two-component QS, known as accessory gene regulator (Agr) QS circuit which relies on the production of AIPs (synthetized from *agrD* precursor) that control virulence factor production and biofilm formation (Parsek & Fuqua, 2004). The AIP transporter AgrB processes the precursor to the mature AIP and also transport molecules outside cell to be are detected by a two-

component signal transduction pathway they are: AgrA and AgrC. (Rutherford & Bassler, 2012). Once the AgrA is phosphorylated, it the promoter P3 and this in turn encoding the RNAIII (agroperon), which post-transcriptionally activates the production of virulence factor and represses the expression of *rot*, which is the repressor of toxins, leading to further expression of virulence factors at high bacteria cell density level (Hsieh et al., 2008; Killikelly et al., 2015).

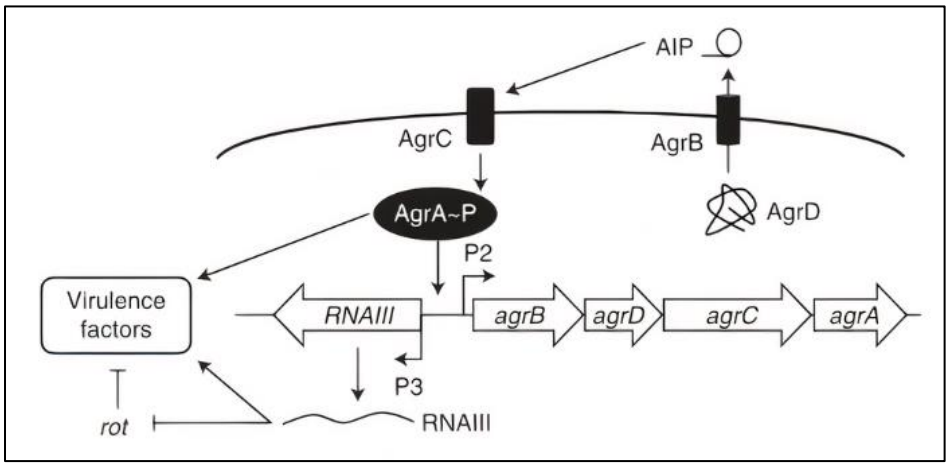

Figure 4. The virulence control system of *Staphylococcus aureus* bacteria (Rutherford & Bassler, 2012).

In the case of the Gram-negative *P. aeruginosa* which can cause recalcitrant multidrug-resistant infections, especially in immunocompromised and hospitalized patients (cystic fibrosis (CF) and non-CF bronchiectasis), associated with chronic lung infections (Maurice et al., 2018). *P. aeruginosa* QS systems, employes three QS systems, two LuxI/LuxR-type and a non LuxI/LuxR-type circuit called *Pseudomonas* quinolone signal (PQS) (Papenfort & Bassler, 2017). Those circuits via the AI synthases (AIs), LasI, RhlI and PqsABCDH, lead to the production and perception of self-inducing signaling molecules such as: *AIs 3OC12HSL, C4HSL,* and PQS, respectively (Rutherford & Bassler, 2012)(Papenfort & Bassler, 2017). Moreover, the cytoplasmic transcription factors *LasR, RhlR,* and *PqsR* detects to the AIs (Rasamiravaka et al., 2015). are responsible for the regulation of the expression corresponding AI synthase and also induce the virulence to the bacterium on the biofilm (Q. Jiang et al., 2019; Malanovic & Lohner, 2016). Although, biofilm formation depends mostly on the environment, it has been showed that QS regulation of rhamnolipids,

swarming and, motility, also contribute to P. aeruginosa biofilm formation. (Rutherford & Bassler, 2012).

Knowing the role of the QS on the virulence of biofilm it is safe to say that, a specific block in the QS signal could be a strategy to avoid the formation of biofilms on surfaces, which can lead to an increase of the sensitivity of pathogenic biofilm to antibiotic agents. In table 5 some studies related to molecular techniques of QS disruption are liested. (Q. Jiang et al., 2019). For instance, external oxidoreductases enzymes have been immobilized on the glass surface because they can affect the biofilm formation and virulence of bacteria. Oxidoreductases affects the AHLs specificity of homologous intracellular receptors (Q. Jiang et al., 2019; Lade et al., 2014) by modifying acyl side chains, thus interfering with the expression of QS related virulence genes, consequently the bacterial biofilm formation of *Klebsiella oxytoca* and *Klebsiella pneumoniae,* as well as the growth rate (Q. Jiang et al., 2019; Wildschut et al., 2006)

Similarly, the RNAIII has been reported to be the QS regulatory effector in *S. aureus*. In this context, an *in vivo* study was conducted by Balaban et. al. (2013). They used a Dacron graft (DG) treated with a linear heptapeptide RNAIII-inhibiting peptide (RIP) to target the peptide-based QS system of *S. aureus* and *S. epidermidis*. The RIP prevents the biofilm formation and in order to determinate the biomaterial-associate infection the DG coated with RIP and different types of antibiotics (implant), was inserted subcutaneously in rats and bacteria were injected intraperitoneal (Balaban et al., 2003). After a week, the implant was removed and by determining the bacterial loads the results showed that the GT-RIP reduced bacterial loads for both, *S. aureus* and *S. epidermidis*. Even when the total inhibition just of RIP was no reached, probably due to the RIP bounding to the DG. The bacterial inhibition results were attribute to the RIP, due to it alone reduced bacterial load by log 3, besides 100% inhibition was reached only when RIP was combined with mupirocin, teicoplanin, or a streptogramin antibiotics which suggest exist a synergism effect among antibiotics RIP (Balaban et al., 2003).

Table 5. Studies related to the QS disruption by several molecular techniques (Q. Jiang et al., 2019).

Models	Bacteria	Anti-QS agents	Target	Effects on biofilm
Synthesis inhibition technique				
In-Vitro, Rats	*Streptococcus pneumoniae D-9*	Sinefungin	Inhibition *ofAI-2* synthesis via downregulating *luxS, pfs,* and *speE* expression	Inhibited pneumococcal biofilm growth in vitro and middle ear colonization *in vivo.*
Receptor inactivation technique				
In-Vitro	*P. aeruginosa*	Flavonoids	Allosteric inhibition of AI-binding receptors, *LasR* and *RhlR.*	Altered transcription of QS-controlled target promoters and suppresses virulence factor production.
Signals degradation technique				
In-vitro	*Pseudomonas aeruginosa* PAO1	N-Acyl-Homoserine Lactone Acylase PA2385	Degradation of 3-oxo-C12-HSL and 2-heptyl-3-hydroxy-4(1H)-quinolone.	Elastase and pyocyanin virulence factors production is reduced

Table 5. Continued.

Models	Bacteria	Anti-QS agents	Target	Effects on biofilm
Antibodies targeting technique				
In-vitro and *mouse model*	*S. aureus*	Antibody AP4-24H11 elicited against a rationally designed hapten	Sequestration of the autoinducing peptide-4	Suppressed *S. aureus* pathogenicity in an abscess formation mouse model *in vivo* and provided complete protection against a lethal *S. aureus* challenge

Abbreviations: autoinducer (AI); enoyl-ACP, enoyl- acyl carrier protein; L-homoserine lactone (HSL); propionyl homoserine lactones (PHL), *quorum sensing* (QS).

3.3.2. Biomaterial-associated infection

As previously mentioned, the first step of biofilm formation is the bacterial adhesion onto a surface of biomaterial. As soon as, the bacteria have colonized the biomaterial, a systemic infection around the biomaterial occurred, better known as biomaterial-associated infection.(Benčina et al., 2018; Li Xu & Siedlecki, 2020) This even lead to biomaterial failure and chronic infection in the host (Arango-Santander et al., 2018). In the clinical or medical practice the biomaterial is consider as an implant, graft or device, hence device-associated infections account for 25.6% of hospital-related infection (HRIs) or nosocomial infection in the United States, and the overall direct cost of HRIs to hospitals ranges from $28 billion to $45 billion annually (Li Xu & Siedlecki, 2020).

The HRIs related to the implant of prosthetic material appears within the firsts 180 days, after clinical intervention (García, 2016). Surgical instruments and medical fluid lines (e.g. scalpels, drips, and catheters) are common sources of biofilm growth (thanks to the present

of aqueous solution, the bacteria in an the environment or the dysbiosis in the host) and subsequent infection in patients (Garrett et al., 2008). The biofilms characteristics during infection have been reported by Donlan et al. (2002), which include that the planktonic cells reaching the bloodstream producing emboli, while, bacterial cells could develop to bacterial resistance via the resistance plasmids exchange within the biofilm, which will reduce the antibiotic efficacy in patients (Donlan, 2002).

Other types of medical devices such as contact lenses, cardiac pacemakers, intravenous or dialysis catheters, heart valves, joint prostheses, or fluid shunts, which are commonly in contact with patient blood, are also in high risks of get biomaterial-associated infection, particularly if there are bacteria attached to the surface of these materials or present in the application area of the device. Table 6 reports common bacterial strains presented in medical devices. For example, the common microorganisms for extended-wear contact lenses are *P. aeruginosa* and *S. epidermidis*, also *S. epidermidis* attach to polymeric devices such as vascular prostheses and total joints, and *S. aureus* to metallic bone implants. In the case of the formation of biofilm on such medical devices, it is difficult to eliminate all the colonies as they are protected by the matrix composed of extracellular polymeric substances (EPS). In these cases, the only solution is to remove the implant from the patient (Taubert et al., 2013).

The most frequent microorganisms involved in biomaterial infections using in patients are bacteria belonging to endogenous bacteria or the commensal community of the skin such as *S. epidermidis* (on polymeric materials) and *S. aureus* (on the surface of metallic devices) (Rimondini et al., 2005). In other cases, skin commensals, such as *S. epidermidis* is commonly reported. This bacterium has a weakly pathogenic potential when it is introduced into the tissues of the host. However, in the presence of foreign material surfaces, it can cause aggressive infections to the patient (Rimondini et al., 2005). Even when there is no information about the biofilm exact mechanism required to form a mature staphylococcal biofilm, this feature can be attribute to the fact that biomaterials/implants are rapidly coated with human serum proteins and Staphylococci have multiple adherence factors that are microbial surface components recognizing adhesive matrix molecules, which bind serum proteins(Patel et al., 2006). Besides, because *S. epidermis* expose PIA

adhesin that is important for the attachment to the cell surface, as well as biofilm formation, surface colonization (Fey & Olson, 2010).

Table 6. Bacterial strains commonly reported on medical devices.

Medical device	Microorganism	Reference
Artificial Voice Prosthesis	Coagulase-negative staphylococci	Donlan, 2002
Central Venous Catheter	Coagulase-negative staphylococci, *Enterococcus spp., Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus*	Donlan, 2002
Intrauterine Device	Coagulase-negative staphylococci, *Enterococcus spp., Staphylococcus aureus*	Donlan, 2002
Artificial Hip Prosthesis	Coagulase-negative staphylococci, *Enterococcus spp., Pseudomonas aeruginosa, Staphylococcus aureus*	Donlan, 2002
Urinary Catheter	Coagulase-negative staphylococci, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus spp., Esherichia coli.*	Donlan, 2002.
Sutures	*Staphylococcus epidermidis, Staphylococcus aureus.*	Rimondini, 2005
Contact Lens	*P. aeruginosa,* Gram-positive cocci	Rimondini, 2005
Cerebral Spinal Fluid	*Staphylococci, Enterococcus spp., Klebsiella pneumoniae, Pseudomonas aeruginosa, Esherichia coli*	Simon, 2018
Peritoneal Dialysis	Bacteria and fungi species	Rimondini, 2005

3.4. APPLICATIONS OF FIBERS IN THE BIOMEDICAL FIELD

Fibers are polymeric materials that refers to any type of fiber, either natural, synthetic or artificial, that represents the basis of textile based materials, being the natural fibers preferred for this applications (Ramawat, 2017). However, there are others manufactured fibers, micro and nano-fibers, which result in engineered fibers or fibrous mats, for reinforce or as composite of scaffolds, hydrogels, wounds and so on (Aibibu et al., 2016). Some fibers applications are presented in the figure 6, which include wound dressings, sutures, nerve conduits, ligaments, and vascular prosthesis.

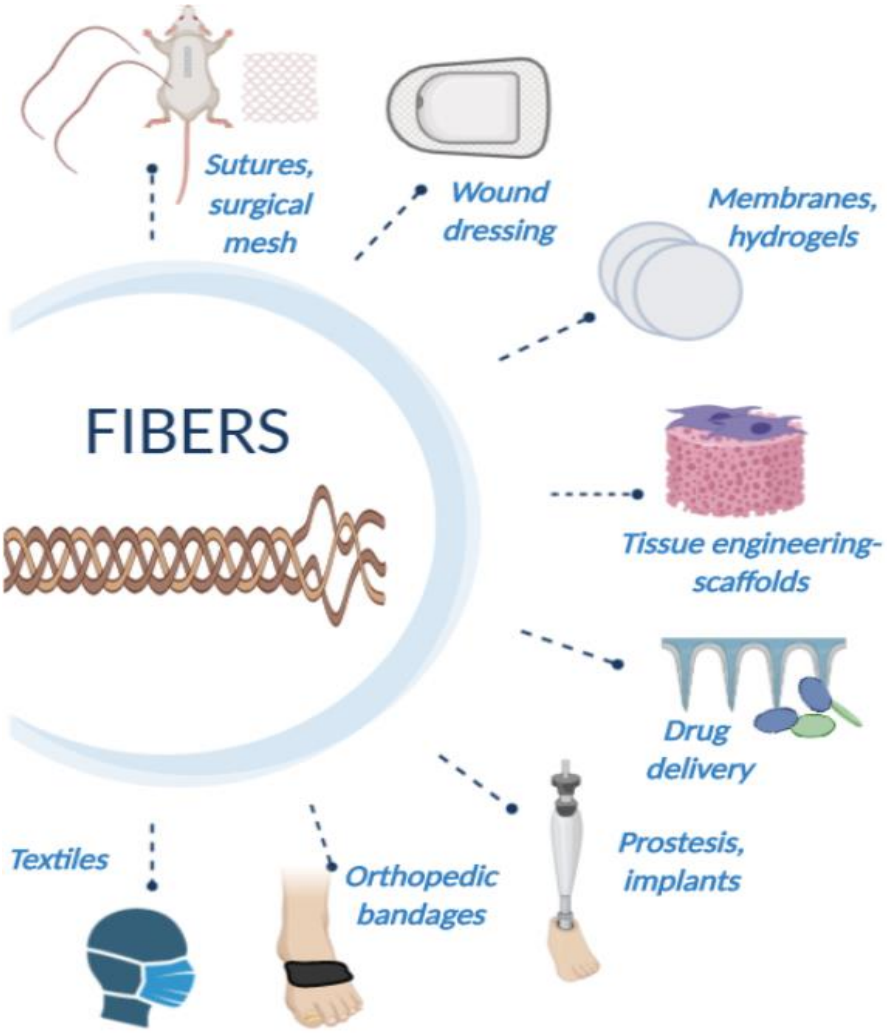

Figure 5. Applications of fibers in the biomedical field

According to Ghori et al., fibers are classified in: natural and synthetic fibers. Natural fibers are from natural sources such as animal, vegetable, mineral, being of the most used jute, flax, raw-date palm fiber, silk, cotton, collagen, among others. As for the synthetic fibers, these include organic and inorganic sources. Being the most common glass, carbon, polyethylene (Ghori et al., 2018). Scientists often try to formulate new functions on many synthetic materials, in order to impart special characteristics, resistance, resilience, and flexibility (Agrahari et al., 2017; Xue & Hu, 2020). Another important type of fibers includes the fibrous mats which can be manufactured via solvent casting, gas foaming, phase separation, emulsion freeze-drying, additive manufacturing (AM), and electrospinning (G. Li et al., 2015). In figure 6 is represented the electrospinning process.

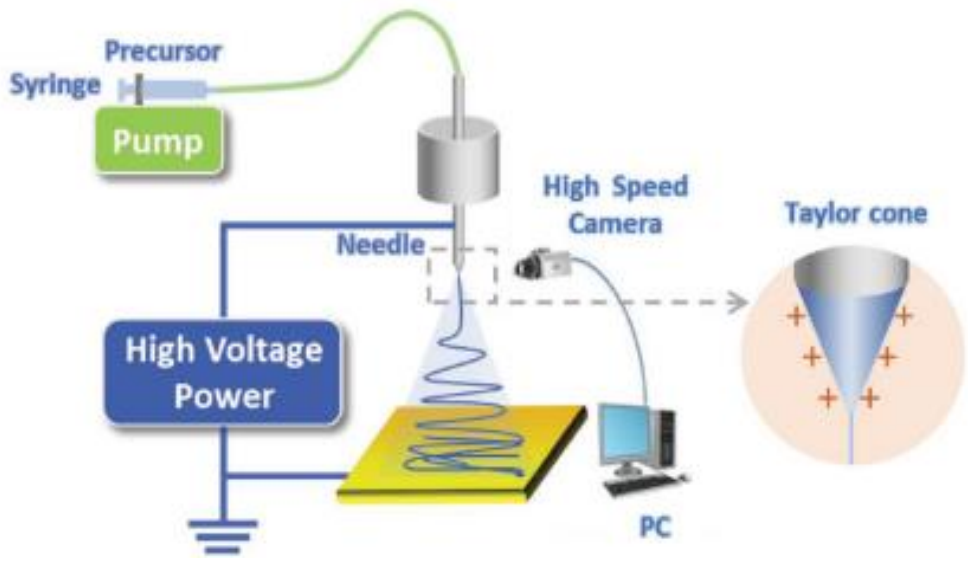

Figure 6. Schematic diagram of the electrospinning process used for micro-nanofibers manufacture (Fu et al., 2018).

Some of the applications of fibers include various therapeutic approaches; gene therapy, chemotherapy, photodynamic therapy, thermal and retention (EPR) therapy, and combination therapy for enhancing localized cancer treatment (Fu et al., 2018; J. Wu et al., 2020). Table 7, describe the major applications of fiber-based polymers as biomaterials. Furthermore, fibers can also be manufactured for wound dressings, bandages, and other body mountable and implanted applications. The most common polymers to create nano/micro fibers include poly(ethylene oxide) (PEO), poly(ε-caprolactone) (PCL),

poly(lactic acid) (PLA), polydioxanone, copolymers including PLGA, poly(vinyl-pyrrolidone) (PVP), and poly (l-lactide-co-caprolactone) silk, collagen and chitosan (Aibibu et al., 2016; Fu et al., 2018; Hiremath & Bhat, 2015; Piconi, 2016; J. Wu et al., 2020).

Table 7. Major applications of fiber-based polymers as biomaterials

Source and Structure	Type of polymer	Reference
Natural polymer • Scaffolds • Hydrogels • Nanofibers • Composites • Textiles • Sutures • Excipients	Collagen*	(Azuma et al., 2015)
	Cellulose*	(Rahmati et al., 2020)
	Resin*	(D. Huang et al., 2020)
	Chitin*	(Azuma et al., 2015; H. Wu et al., 2017; Zhang et al., 2019)
	Silk*	(Defrates et al., 2018; Ghezzi et al., 2013; Xue & Hu, 2020)
Synthetic polymer • Sutures • Catheters • Membranes • Artificial skin • Contact lenses • Scaffolds	Polyglycolide (PGA)*	(Boncu et al., 2020; Hiremath & Bhat, 2015)
	Polylactic Acid (PLA)*	(B. Li et al., 2020)
	Poly(L)-lactic acid*	
	Polylactic–glycolic acid (PLGA) *	(Said et al., 2011; Taubert et al., 2013)
	Nylon*	(Piconi, 2016)
	Poly(Ethylene Glycol) (PEG)*	(Taubert et al., 2013)

*FDA approved for clinical use on humans.

Nowadays, nascent studies of fibers for biomedical applications have increased. In the last 11 years the tendency of fibers studies is to increase. Figure 7 shows that by the 2010 year appear 238 studies regarding to fibers in the biomedical field and by 2019 this quantity was triplicated, with more than 600 scientific publications.

The demand for fibers has increased due to the properties of fibers including quick processing, controllable biodegradability, remarkable mechanical properties, biocompatibility, to mention a few (G. Li et al., 2015). The fibers research associated with, include more than 3000 peer-reviewed publications from PubMed and SciFinder database (figure 7), from 2011 to current days, provide evidence of the rapidly increase in this field.

To illustrate this amount of research published, a comprehensive overview of applications of different types of fibers for the medical field will be divided into: non-implantable materials, implantable materials, extracorporeal implants in the following sections (Gorgieva et al., 2018)

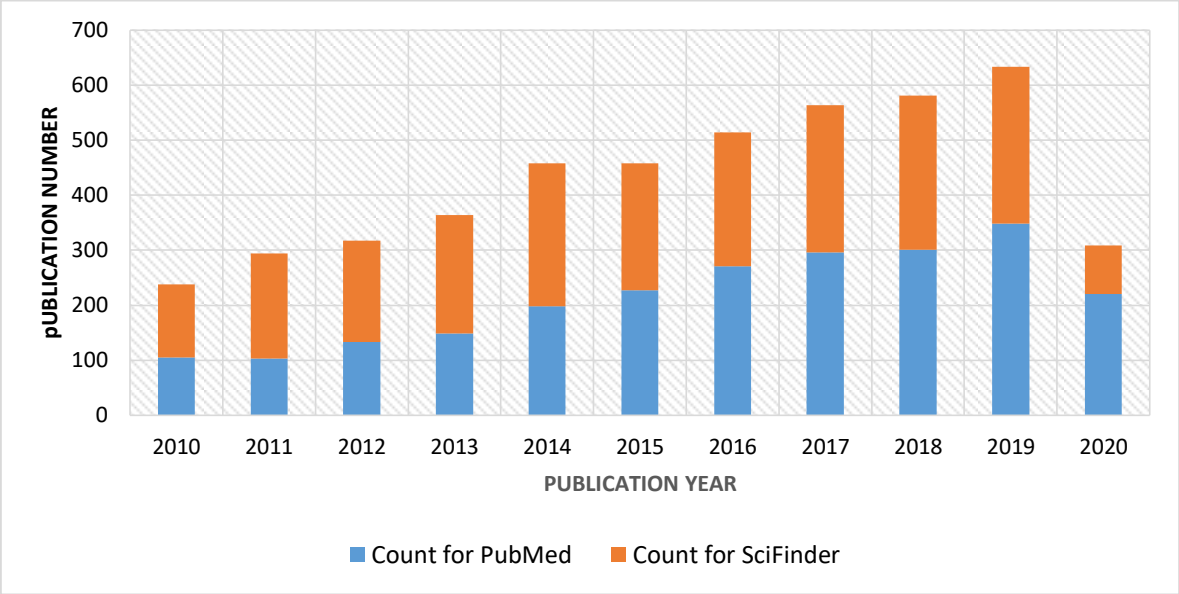

Figure 7. Publications on fibers-based biomaterials for the biomedical field over the last 11 years. Data searched from SciFinder and PubMed. Search query: biomedical and fibers (SciFinder), biomedical applications and fibers (PubMed).

3.4.1. Non-implantable materials

Biomaterials used for external applications on the body, are named non-implantable materials. Those materials include wound dressings, orthopedic bandages, pressure garments, and prosthetic socks, among other examples (G. Li et al., 2015). A current example is the ocular repair dressing, BIOcular™, which is a surgical suture composed of biopolymeric hydrogel and various chemistries of nanofibers (NF), to achieve an array of resultant properties. First, the hydrogel provides control release and NF offers mechanical, optical, and biological properties on the material. The function of BIOcular™ is to treat corneal abrasions and ulcers on the surface of the eye, as well to provide compatibility, allowing a transmission of 85% of visible light and effectiveness in of antibacterial properties on biomaterial-tissue interface The dressing material can also be loaded with antibiotics and antimicrobials, for treating persistent corneal ulcers (Agrahari et al., 2017; Luna Innovations Incorporated, 2013; Tison, 2013). Similarly, Biobrane® which is a commercial artificial skin patch made of two layers (Callaway et al., 2018), an inner layer of nylon mesh (semi-crystalline synthetic polymers with polyethylene segments), and an outer one of silastic (Smith-nephew.com, n.d.). The inner layer serves for allowing fibrovascular ingrowth and the silicon layer on the outside serves as a vapor and offers protection against bacteria penetration in the skin (Gorgieva et al., 2018).

In terms of the natural fibers, silk-based materials have been used by its remarkable mechanical strength, flexibility, low immunogenicity, high oxygen permeability, and overall good biocompatibility (Callaway et al., 2018). Silk-based materials are composed by repeating amino acid sequences and interactions (glycine-alanine/serine dipeptides) (Najjar et al., 2017). Najjar and colleagues (2017) developed a novel energy harvester by integrating electrospun Poly (vinylidene fluoride-co-hexafluoropropylene (PVDF-HFP) copolymer nanofibers with flexible substrates. These nanofibers are based in SF-glycerol composite (silk fibroin, with 20% of glycerol), moreover, by analyzing the stress-strain curve these nanofibers provide a desirable and balanced mechanical behavior in terms of flexibility and strength (Najjar et al., 2017). Also, the estimated yield strength of 1.3684 MPa and ultimate strength of 2.6711 MPa demonstrate that the SF-glycerol composite is a strong material and can stand strong forces and greater elongation, compared to only the SF

that that exposed elastic and plastic regions (yield strain and strength are estimated as 0.4350 and 2.0833 MPa). Those properties of nanofibers suggest a biocompatible silk/polymer skin mountable device with approaches for wearable electronics, due fibroin is a flexible interfacial components in electronic and photonic devices (e.g. biosensors, metamaterial silk composites, and in vivo bio- trackers/detectors) (Koh et al., 2015; Najjar et al., 2017).

Other than silk materials, there are other natural fibers which are protein-based fibers coatings and films (e.g. collagen and elastin) (Jao et al., 2017; Piconi, 2016). When these fibers are combined with drug treatment, the fibers use can be continuous on the patient while reducing the risk of infection from multiple treatments and drug admissions (Elashnikov et al., 2016; Jao et al., 2017). Sahiner et al. (2014), developed a collagen-based hydrogel film prepared with metal nanoparticles (Ag and Cu) loaded with drugs such as gallic acid (GA) and naproxen (NPx). The hydrogen film has been used because they have good antimicrobial properties against *Escherichia coli, Bacillus subtilis,* and *Staphylococcus aureus* (Sahiner et al., 2014).

As described previously, both synthetic and natural polymers (Chen et al., 2018) and fibers are not commonly used individually, but rather as “hybrid” from different nano-micro materials, to yield a synergistic effect on the biomaterial depending on its use (Aibibu et al., 2016; X. Li et al., 2019). Table 8 show the major fibers-based biomaterials reported literature.

Table 8. Major fibers-based biomaterials reported in literature from (2010-2020 years)

Product	Material	Application/Aim	Reference
Non-implantable materials			
Micro/nano-fibers	PMMA nanofibers doped with AgNPs and TPP	Potential light-triggered material with antibacterial activity against *S. epidermidis* and *E. faecalis*	(Elashnikov et al., 2016)
	PLGA nanofibers	Antimicrobial PLGA ultrafine fibers, interaction with wound bacteria	(Said et al., 2011)
	Biobrane*	Artificial skin patches, made up of nylon mesh and silastic, for re-epithelialize the skin after burn.	(Smith-nephew.com , n.d.)
	SF-glycerol composite	Biocompatible silk/polymer skin mountable device with approaches for wearable electronics.	(Najjar et al., 2017)
Hydrogels/scaffolds	BIOcular-Bandages*	Nanofiber-reinforced hydrogels for ocular repair	(Luna Innovations Incorporated , 2013)
	Collagen-based hydrogel films	Drug-delivery devices for potential wound dressing materials (GA) and (NPx), with antibacterial properties against *E. coli, B. subtilis*, and *S. aureus*	(Sahiner et al., 2014)

Table 8. Continued.

Product	Material	Application/Aim	Reference
Implantable materials			
Sutures	Catgut: chromic catgut* Polyglyconate: Maxon* Polydioxanone: PDS*, PDX*, Surgricryl*.	Monofilament absorbable suture material for gastrointestinal surgery.	(Kreszinger et al., 2018)
	PET monofilament	PET monofilament grafted with plasma for acryliyc acid provides antibacterial properties against *E. coli* and *S. aureus*	(Gupta et al., 2001)
Tissue-engineering	AuNps embedded in biodegradable PLGA electrospun membranes.	Coating material for preventing implant associated infections against *S. aureus* and *E. coli.* Made up of PLGA electrospun membranes containing 0.5 wt% of AgNPs (considered as the most suitable combination for clinical applications)	(H. Wang et al., 2013)
	eTF scaffold biofunctionalized with tropoelastin	Vascular Graft, which presented strength and stiffness within the range of those of native blood	(Oliveira et al., 2020)

	at the luminal surface.	vessels.

Table 8. Continued.

Product	Material	Application/Aim	Reference
Drug-delivery	PEG-PLA nanofiber matrix	Drug delivery system of DOX by diffusion and degradation of fiber matrix for cancer treatment: Human hepatocarcinoma SMMC-7721cells.	(Fu et al., 2018)
	Linezolid loaded PLGA nanofibers	Linezolid loaded implantable PLGA nanofibers with antibacterial properties against MRSA, and tunable for TE. For possible orthopedic and dental infection.	(Boncu et al., 2020)
	Triblock copolymers	Drug model was paracetamol, and the controllable release profiles, make this fiber as potential implantable drug carriers.	(Agrahari et al., 2017)
	Porous collagen-based (CAC) scaffold	CAC with alginate polymer using rhodamine B as the model drug. Also, it can be tuned for TE applications due allows proliferation of osteoblast-like cells (MG63) seeded on CAC scaffold.	(Jao et al., 2017)

Table 8. Continued.

Product	Material	Application/Aim	Reference
Extracorporeal implants			
Polymyxin-B		Used cartridge in which polystyrene-based fibers are functionalized with covalently bound PMX for remove circulating endotoxin by adsorption for patients with hemoperfusion.	(Clark et al., 2018; Cruz et al., 2007; De Rosa et al., 2019)
Interventional Lung Assist (iLA)*		Carbon dioxide removal ($ECCO_2R$) in the form of bicarbonate ion.	(Hazfiza et al., 2016)

Abbreviations: Silver nanoparticles (AgNps), polymethyl methacrylate (PMMA), meso-tetraphenylporphyrin (TPP), silk fibroin (SF), poly(lactic-co-glycolic acid) (PLGA), Electrospun tubular fibrous (eTF), gallic acid (GA), naproxen (NPx), doxorubicin (DOX), polyethylene glycol (PEG), polyethylene terephthalate (PET), polylactic acid (PLA), poly(l -lactide-co-d,l -lac- tide) (coPLA), Quaternized chitosan (Qch), tissue engineering (TE), methicillin-resistant *Staphylococcus aureus* (MRSA),

*Available in the market. Find more available hollow fibers membranes in: (Cobetter Filtration Equipment, 2014). https://cobetterfiltration.com/Industries/Medical/OEM-Membranes-and-Devices/

3.4.2. Implantable materials

Implantable materials refer to devices that are placed inside the body. These materials are used for wound closure or replacement surgery. This includes sutures, soft-tissue implants, orthopedic implants, vascular/hip, and knee prostheses (Chen et al., 2018; G. Li et al., 2015). Because these materials are intended for *in vivo* applications (X. Hu et al., 2012), they should strictly meet biocompatible and hemocompatibility criteria, cellular adherence,

adequate porosity and mechanical properties, cellular growth and non-toxic manufacture techniques (Gorgieva et al., 2018).

In the field of tissue engineering (TE) to comply with the above requirements, the commonly structures used include mainly 2D and 3D composites/scaffolds (X. Hu et al., 2012). These structures are prepared by techniques such as electrospinning, it is a manufacture technique to prepare fibrous mats, and it is the most remarkable and used technique for include micro and nano-fibers in different materials or alone, in a generic term electrospun-based materials (Fu et al., 2018; Hiremath & Bhat, 2015). These materials are employed to delivery drugs and nanoparticles (NP) (X. Li et al., 2019) along with the desired specifications such as size, morphology, and molecular weight (Defrates et al., 2018).

Electrospun-based materials are affected by the nanofibers chemistry, first because these fibers are prepared from a viscous polymer solution by electrostatic charges among the needle or tip and the collector (Figure 6) (X. Hu et al., 2012). Besides, those electrospun-fibers (EF) can be loaded with additives either hydrophobic or hydrophilic materials, for the regulation of drug release from nanofibers. The chemistry of EF is a determining factor in wetting behavior and degradation rate of fiber (Chen et al., 2018).

Aramwit and colleagues (2015) developed a scaffold for wound healing made of silk sericin and polyvinyl alcohol (PVA). The authors also improved physical and adhesion properties of the wound healing by using glycerin. The silk sericin/PVA scaffolds with 2% wt/vol glycerin, were used as a biocompatible (subcutaneously implanted in rats, with no irritation), more flexible, and less adhesive wound dressing comparing to the scaffold without glycerin. The silk sericin/PVA scaffolds provide long-term healing of wounds because it provides a controlled release of silk sericin (SS) than the scaffolds without glycerin. This SS realease activate the healing of wounds by the proliferation of skin cells, such as keratinocytes in the rat (Aramwit et al., 2015).

Moreover, another approach based on electrospun fibers (e.g. hydrogels, membranes) have been used for drug delivery applications based on electrospun fibers (Liu et al., n.d.; J. Wu et al., 2020). However, some limitations of the uses fibers materials are related to the

absence of bioactivity and antibacterial capacity on the material (X. Li et al., 2019. For instance, poly (L-lactic acid) (PLLA) was functionalized by B. Li et al. (2020) to overcome such limitations. They developed a dopamine-functionalized reduced graphene oxide (rGO)/PLLA composite with possible uses for drug delivery and tissue engineering. This composite was loaded with tetracycline hydrochloride (TC) drug (TC/rGO/PLLA) to provide antibacterial activity in the material, it approach was evaluated against *E. coli* and *S. aureus* via inhibition zone assays. The results exposed the highest bacterial inhibition of both strains was by the TC/rGO/PLLA nanofibrous mats, in comparison with PLLA, GO / PLLA, and rGO / PLLA (B. Li et al., 2020). This findings suggest that, fibers loaded with antibiotics could be used as an antibacterial coating or as an implanted scaffold to prevent biomaterial-associated infections (J. Wu et al., 2020).

In the case of sutures, a wide range of natural fibers sources of fibers have emerged, recently including the usage of silk, chitin (H. Wu et al., 2017), chitosan (Azuma et al., 2015), catgut (sheep intestine) (Gorgieva et al., 2018; Karabulut et al., 2010; Kreszinger et al., 2018). The use of the type of material depends on the suture to be applied which can be classified as non-absorbable or absorbable suture. The absorbable suture is can be absorbed on the tissues over the year (Karabulut et al., 2010; Zhang et al., 2019). It is noteworthy to mention, that the final choice of suture material for tissue closure will be based on its properties, including initial tensile strength, duration of tensile strength retention, and deformability (Kreszinger et al., 2018).

3.4.3. Extracorporeal implants

Extracorporeal implants are artificial organs that are used for blood purification and include artificial kidney, artificial liver, and mechanical lung. (Gorgieva et al., 2018; G. Li et al., 2015). The extracorporeal or *ex vivo* applications and their use have increased owing the long wait times for organ transplants due to the reduced number of organ donors available. (Orizondo et al., 2019; Madhani et al., 2018; Kim et al., 2011). The role of fibers in this uses are mainly for the manufacture of membranes, which are responsible for purification

procedures. For instance, blood contact membranes are used for apheresis procedures; it is critical to suppress the tendency of the surface to adsorb blood proteins (e.g.; fibrinogen and albumin), which can lead to blood thrombus formation or coagulation in the patient (Taubert et al., 2013).

Most of the purification/gas exchange processes use hollow membranes (HM) and require blood compatibility, selectivity, and fouling resistance (G. Li et al., 2015). The HM are mainly based on regenerated cellulose and polysulfone (PSu) or polyethersulfone (PES) that are hydrophobic polymers, those are commonly combined with hydrophilic additives, such as poly-vinylpyrrolidone (PVP) to provide high blood compatibility, selectivity and fouling resistance to HM (Beek et al., 2020).

For the hemodialysis (HD) treatment, extracorporeal implants are currently used during end-stage renal disease patients, that is when the organ (e.g. kidney) can no longer eliminate the body toxins on its own. In this regard, Namekawa et al. (2014) fabricated a zeolite–polymer composite nanofibers for removal of uremic toxins from kidney failure patients. The nanofiber was made of poly (ethylene-co-vinyl alcohol) (P-EVOH) as the main matrix, is a blood compatible polymer, and also composed of zeolites that can adsorb uremic toxins from the body (i.e. creatinine) (Namekawa et al., 2014). Similarly, Beek et al. (2020) developed hollow fibers with no additive leaching by blending PES with small amounts of a randomized copolymer consisting of N-vinylpyrrolidone (NVP) and N-butyl-methacrylate (BMA), which is a membrane currently available in the market SlipSkin™ (SS), it has very good blood compatibility. The developed fibers can reach high removal of a wide range of uremic toxins (creatinine and protein-bound uremic toxins) while depicting excellent fouling resistance (Beek et al., 2020). This performance is avantegoues in the patients for avoiding significantly fiber-protein interaction, which means no proper water and proteins flux, during the purification process. (Beek et al., 2020)

Other than biomedical applications, fibers are widely used in industry, automobile, textile, environmental and biotechnological applications. As they can be incorporated for reinforcing materials to provide mechanical, biological properties. Table 9 show more major applications of fibers in various industries and fields.

Table 9. Major applications of fibers given the industry/field of application (Ahmadi et al., 2018; Al-oqla et al., 2014; Ashraf et al., 2019; G. Li et al., 2015; Ramawat, 2017).

Industry or field	Application purpose	Type of material
Automobile industry	To reinforce materials to provide different mechanical properties	Nanofibers, palm fiber, cabuya fiber, coir, jute, sisal. abaca fiber
Biotechnology industry	To immobilization of bacteria to decontamination of polluted water. To immobilization of enzymes for the production of desired proteins. To decontamination of pollutants in the air, residual waters.	Pineapple fiber, jute fiber, sisal fiber, palm fiber, cotton fiber, carbon fiber, silk fiber, abaca fiber, nanofibers.
Textile industry	Silk fibroin finishing agents; coated with antimicrobial substances for hospital, surgical textile fabrics (face masks, gowns/wear). To create biodegradable and sustainable textiles.	sisal fiber, palm fiber, cotton fiber, silk, abaca fiber, microfibers

3.5. NATIVE FIBERS

3.5.1. Ecuadorian native fibers and economic considerations

Ecuador is a country with a high diversity of raw various biomaterials such as natural fibers. These materials can be extracted from plants vegetations, including plants commonly identified such as cabuya, totora, abaca, ceibo, palms, toquilla straw, cotton, to mention a few. In th case of non-vegetation sources or animal sources, the biomaterials can

be extracted mainly from sheep, alpaca, and rabbit. Figure 7 shows examples of vegetation sources of biomaterials The use of natural fibers has been beneficial to the environment since the biomaterials are known to be renewable, ecofriendly, and highly biodegradable (Ramawat, 2017) in comparison with synthetic filamentary products that could be take up to 5000 years to degrade in the environment (Inter Press Service, 2000).

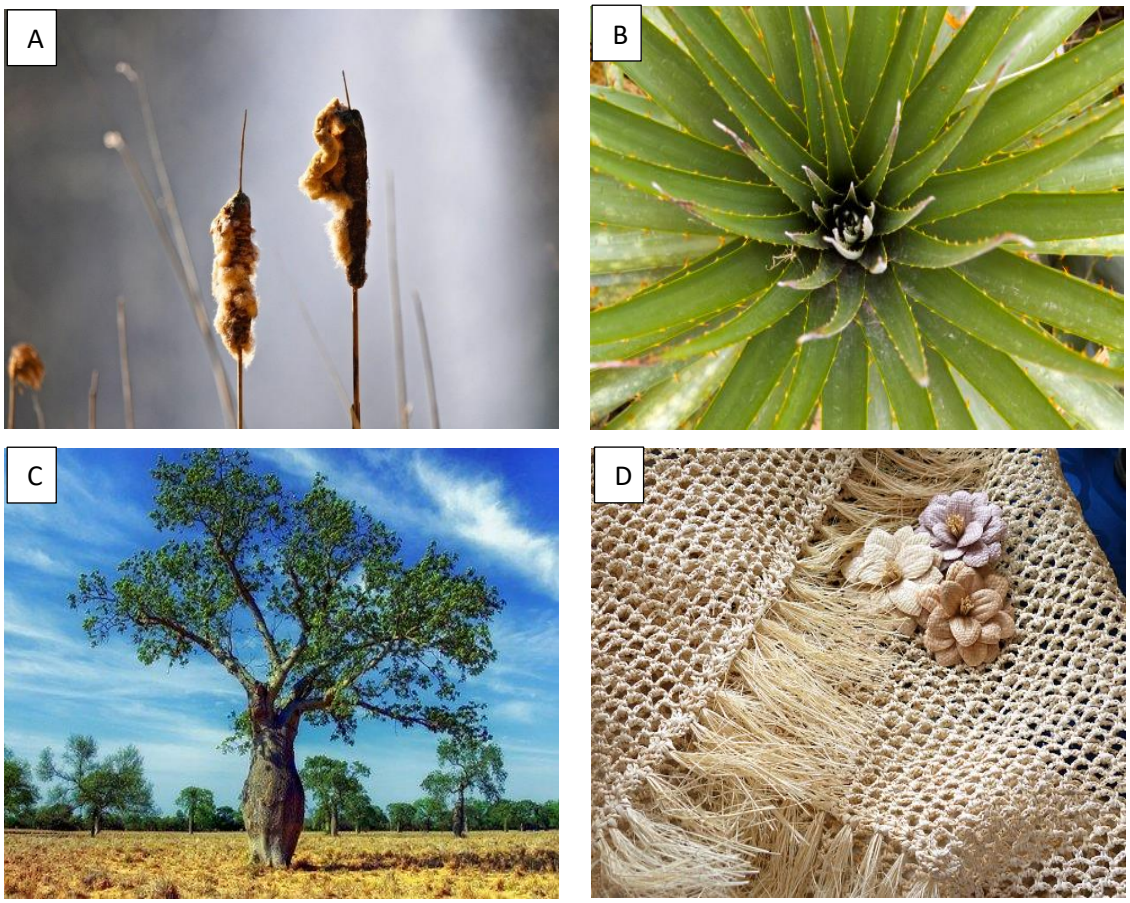

Figure 8. Types of Ecuadorian sources for fibers. Common names of fibers: totora (A), abaca (B), ceibo (C), toquilla straw (D). (Pixabay.com, 2020)

According to a report by the Center for Information and Commercial Intelligence (Centro de Información e Inteligencia Comercial, CICO) in 2009, Ecuador ranked in the 33rd place in the world of exporters of ropes and cordage of the *agave genus* (e.g. jute, sisal, cabuya, among others) it represents a participation of 0.27% of world exports (Centro de Información e Inteligencia Comercial- CICO, 2009). Moreover, in a more recent report by the Revista Gestión (2019), Ecuador ranked second, just below the Philippines in fiber production and exports (Cobos, 2017). Being the agave related products the sixth primary

major export in 2019 in the country and for 2020, the rank has moved up the fifth place. Figure 8 shows a timeline of the Abaca export for the last eleven years. Interestingly, the main export market of Ecuadorian fiber is the Philippines, as this country is both a producer and re-exporter of the abaca to all over the world, then it occupies the first place of abaca worldwide exporter.

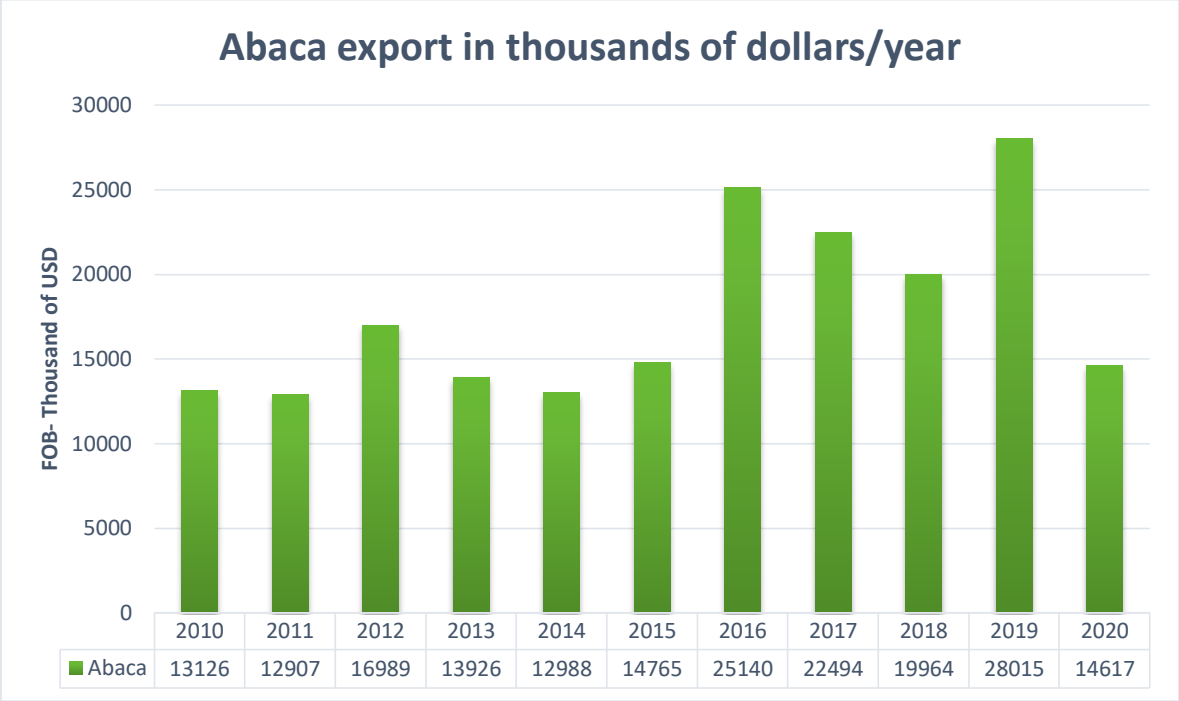

Figure 9. The economic impact of abaca (*Musa textilis*) exportation in thousands of dollars in the last 11 years (Banco Central del Ecuador, 2020). In Ecuador, abaca is the most exported fiber and is the second-largest exporter of abaca worldwide. (FOB: free on board)

In Ecuador, abaca is the most exported fiber and globally it is the second-largest exporter of abaca. Even when these sales represent less than 0.01% of total exports (Cobos, 2017), it is important to consider that they are among the primary export products, along with bananas, coffee, and shrimp.

In addition to generating an economic impact through exports, the textile sector from Ecuador produces numerous related jobs. In fact, this sector represents the biggest manufacturing sector that employs 158 thousand people, just behind after the food sector.

drinks and cigars. Furthermore, the textile and clothing industry is also associated with a total of 33 productive small sectors (Asociación de Industriales Textiles del Ecuador, n.d.).

Various organizations have been developed to create an impact in the industry of textiles. For example, the Association of Textile Industries of Ecuador, is conformated by some companies such as Francelana S.A., Enkador S.A., Empresas Pinto S.A., among others. There are also organizations focused on abaca manufacturing only, the largest being Furukawa Plantaciones C.A. (Table 10). Furthermore, in 2000 the Center for Research and Industrial Development of Natural Fibers was created in Ibarra (Centro de Investigación y Desarrollo Industrial de Fibras Naturales). It is center associated with the "Universidad Católica, sede Ibarra". This center has being guided by Ryszard Kozlowski, director of the Institute of Natural Fibers of Poland (Inter Press Service, 2000), to incentive the cultivation and manufacture of natural fibers in Ecuador, by promoting the investment to develop two major projects; the first one is the installation of a pulp and paper factory, and the second one is to install an abaca yarn plant (Castellanos, 2010).

Table 10. Ecuadorian companies that produce and export abaca fiber (Cobos, 2017).

Company's name	City	Emp*	Sales revenue ($)	Asset ($)	Patrimony ($)	Utility ($)
Furukawa Plantaciones C.A. Del Ecuador	Santo Do-mingo	174	9.236.830	17.372.571	15.433.527	715.000
Textiles Texsa S.A.	UIO*	90	5.555.605	10.874.426	9.941.152	643.340
S'lealschl Internacional S.A.	GYE*	7	0	800	800	0
Compania Agrícola Y Pecuaria El Colorado Comapelco S.A.	GYE	4	0	446	446	0

***Abbreviation: GYE: Guayaquil; UIO: Quito; Emp: employees**

Some of the advantages of using natural fibers include health benefits, sustainability, technological benefits (e.g. mechanical properties), as well as the direct impact of the related industries in creating employment (e.g. farmers, manufacturers). Additionally, the fiber business is responsible for promoting fashion (eco-fashion) among consumers. For example, coconut fibers have been used for making mattresses which provide biocidal effects against fungi and mites. Similarly, hemp (*Cannabis sativa ssp. sativa*) fibers have antibacterial properties, and studies show that the most hygienic textile for hospital sheets is linen. Another advantage of natural fibers is that they are renewable raw materials and during the manufacturing process no CO_2 emissions are produced (Centro de Información e Inteligencia Comercial- CICO, 2009). Furthermore, harvesting a ton of jute fiber requires less than 10% of the manufactured energy compared to the production of polypropylene (Centro de Información e Inteligencia Comercial- CICO, 2009). Likewise, the cultivation of manila hemp (*Musa textilis*) reduces soil erosion levels and reduces rainfall impact, decrease evaporation and obtain a better soil cover and rehabilitates biodiversity in tropical areas, while its waste is used to fertilize other plantations (Cobos, 2017; Hilger et al., 2013)**.**

In Ecuador, the fibers have been used for the elaboration of compounds reinforced with natural fibers, in such a way that their mechanical properties have been characterized, including resistance to traction, bending, and impact. In table 11 is detailed some of the studies or theses that show the various uses and approaches for fibers in Ecuador.

Table 11. Ecuadorian studies of fibers-based materials for different areas.

Area	Approach	Fiber	Ref.
Industry (automotive and civil)	Matrix reinforced with fibers	Cabuya, Banana peel fiber, coir, african palm fiber, guadua, mocora. bamboo, sawdust, nylon, abaca	(Daniel Armas, 2017; David Armas et al., 2016; Belduma, 2018; Imbaquingo, n.d.; Llanes et al., 2019; Navarrete, n.d.; Nicolalde et al., 2019; Pachacama, 2015; Proaño, 2015; Pucha, n.d.; Pulloquinga, 2019; Tamayo, 2012; Valarezo, 2013)
Biotechnology	Filter matrix for decontamination and immobilization	Cabuya, polyacrylonitrile, coconut fiber, kenaf	(Alexis & García, 2019; Arturo, 2017; Salazar & Núñez, 2017)
Biomedicine	Wound dressings, sutures	Chitosan fibers, silk fibroin, cellulose fibers	(Alexis et al., 2019; Alexis & Romero, 2019; Altamirano et al., 2018; Benavides, 2019; Tapia et al., 2018)
Manufacture and textile industry	Textile	Cotton, cabuya	(Betancourt, 2018; Rojas, 2016; Salas, 2016)

3.5.2. Natural fibers and bacteria interactions

Natural plant fibers have a biopolymer composition (mainly lignin, pectin, and hemicellulose), so in some cases it is necessary to extract these polymers to obtain fine fibers (Bous et al., 2018). Lignocellulose fibers are suitable as substrates for biofilm adhesion because they have comparable surface area per unit volume, while having high porosity, low specific gravity and slower degradation rates (Chanakya & Khuntia, 2013).

At first sight, the biofilm formation process on fibers complies the same 3 stages elucidated previously, which include the adherence, accumulation, and dispersal (Figure 1, page: 6). Kapellos et al. (2015), explain that because of the structure of fibers: high specific area (HSA) and the complicated geometry and topology of the fluid-solid or other fluid-fluid interfaces that are colonized by microbial cells, various porous models have been developed (e.g. flow chambers packed with glass beads and planar pore networks etched in glass) for biofilm formation research (Kapellos et al., 2015). Then, the parameters mediating the fiber biofilm formation are: characteristic pore size, characteristic velocity of the fluid in the pores, density and viscosity of the fluid, and the hydraulic permeability of the porous biofilm.

In a recent study performed by Aufrecht and colleagues (2019), used a microfluidics porous platform for study the bacterial movement and biofilm formation of the wild type (WT) or EPS defective mutant (ΔUDP) of *Pantoea sp.* YR343. They discover that the bacterial transport across pore space velocity gradients influence the initial bacterial and surface attachment. Besides, the gravity influences the flow conditions in the microfluidics platform, that flow activated the ability of the bacteria to produce extracellular polymeric substances, which will influence the spatial distribution of the bacteria in the porous medium (Aufrecht et al., 2019). Similarly, Sankaran et at., (2019) investigate the influence of molecular size on diffusion within microcolonies of *P. aeruginosa* in the biofilm matrix. The discoveries suggest that as the microcolony increase in size, the reduction of the pores size occurs, i.e. the average thickness of biofilms showed positive correlation with the size of the pores, with larger pores hosting thicker biofilms (Kapellos et al., 2015; Sankaran et al., 2019)

The literature reports several cases of biofilm formation in plant fibers (Derakhshan et al., 2018) (coco, jute, palm, flax), (coconut, jute, palm, flax), which have uses in the biotechnology industry (Table 9, page 42), especially for bacterial immobilization (Hajieghrari & Hejazi, 2020; Rauf et al., 2020). Bacterial immobilization is understood as the physical location of the bacteria in a specific region, naturally or induced, in which the bacteria are able to maintain a desired catalytic activity (Garzón & Barragán, 2008), he main objective of this immobilization in fibers is bioremediation, such as wastewater cleaning, drug removal, absorption of heavy metals, among others).

Bacterial cells are naturally immobilized, initially by bacterial trapping in the pores of the fibers (Garzón & Barragán, 2008). A porous medium is known to provides an environment to host biofilm-forming bacteria because of its high specific surface (ratio of the matrix wetted surface area to the matrix volume) (Kapellos et al., 2015).

The way studies with microfluidic porous platforms have been established is comparable to studies of fiber functionality with immobilized bacteria for biotechnology applications and can be extended to studies involving the use of plant fibers (Hajieghrari & Hejazi, 2020; Rauf et al., 2020; Kapellos et al., 2015).

In the area of biomedicine, plant fibers have been studied as biomaterials with a focus on their antibacterial properties. For example, Rocky and Thompson (2019), used 4 different types of bamboo fibers (e.g. bamboo viscose fibers, woven fabric (Dharma Trading Co.), and two samples of raw bamboo (dry and fresh) and the fibers were manufactured by two extraction methods (chemical and enzymatic)(Rocky & Thompson, 2019). Then, their antimicrobial properties were evaluated (against *S. aureus*) using spread plate method (SPM). SPM was measured by optical density (OD) and the count of colony forming units (CFU). The results of this study revealed that all bamboo fibers, extracted with chemical and enzymatic processes showed inhibition of *S. aureus*. However, the fibers labeled as CPE-XI (1000 CFU/ mL) and CP-I (1800 CFU/mL) had excellent prevention of bacterial colony formation. Figure 10 shows the agar plate test. These properties in the two specimens, are attributed to the process of fiber extraction. CPE-XI used an enzymatic treatment (ET) for delignification, and its antibacterial activity is attributed to ET resulting in not well-delignified fiber, and it is known that bamboo lignin has antimicrobial

properties (Rocky & Thompson, 2020). Then, in the case of CP-I which had a chemical treatment with a solution of NaOH (6 g/L), H2O2 (6g/L) and 20 mL/L of fabric softener, its antibacterial capacity is attributed to the removal of lignin, pectin, and other compounds to a certain degree improved the antibacterial activity of natural bamboo fibers (Rocky & Thompson, 2019).

Figure 10. The growth of microbial colonies on various specimens using the spread plate method (Rocky & Thompson, 2019).

Likewise, Ilangovan et al. (2018) fibers extracted from stems of *Curcuma longa L.* plant (turmeric fibers) via alkali treatment (using NaOH), for obtaining small fiber bundles. The authors studied the antimicrobial properties against gram negative and positive bacteria, the composition, and the mechanical properties of the treated turmeric fibers (TTF) (Ilangovan et al., 2018). The composition of TFF was confirmed by the lignocellulose patter seeing by X-ray diffraction showed the treated fiber has cellulose (50%), lignin (12%), and ash (10%), besides the crystallinity was about 33% compared to 30% in the untreated stalks. The TTF showed good performance of antibacterial activity against *E. coli and S. aureus*, (50 and 59% of inhibition). Finally, the tensile strength, 325 MPa is comparable with the jute fibers (400–800 MPa), all these characteristics make TTF desirable for biomedical applications (e.g. wound dressing, suture, etc.) (Wambua et al., 2003)

Also, the properties of natural cellulose fibers have been studied with a view to applications such as surgical sutures. Alexis & Romero (2019) reports natural cellulose fibers with tensile properties (138.84 MPa of UTS) comparable to silk (564.78 MPa of UTS),

biodegradable and antibacterial. (Alexis & Romero, 2019). In addition, Kandimalla et al. (2016) conducted a *in vivo* study of novel suture fiber from ramie plant (*Boehmeria nivea*). (Kandimalla et al., 2016) The fibers passed thought a gum, pectins removal and also alkali extraction process, the final fibers were reeled together by five-loobraiding technique to fabricate the suture material. The antibacterial properties were evaluated, as well as the tensile properties, biocompatibility and wound closure efficacy in comparison with market available BMSF suture. The results were that fiber suture showed inhibition against *E. coli*, *B. subtilis and S.* aureus, besides the *in vivo* assays, performed in rats biocompatible towards human erythrocytes and nontoxic to mammalian cells, besides the histological results confirm the rapid synthesis of collagen, connective tissue.

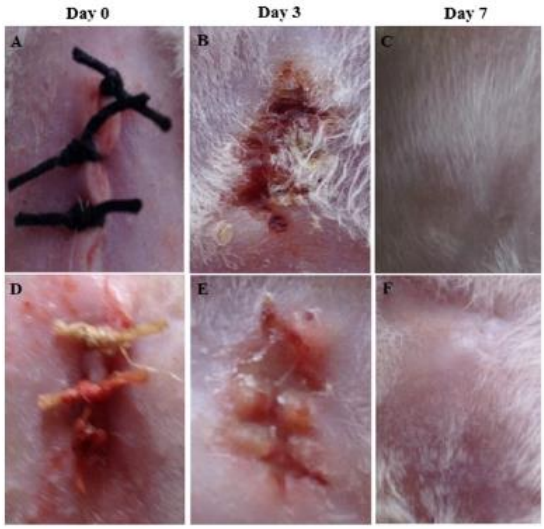

Figure 11. Surgical wound closure of animals with BMSF suture (A, B, C) and ramie suture (D, E, F) and evaluation of wound healing efficacy at various observation periods (0th, 3rd and 7th day) (Kandimalla et al., 2016).

4. CONCLUSIONS AND RECOMMENDATIONS

The elucidation of the mechanisms by which biofilms are formed and survive has a wide contribution for the areas that benefit from these discoveries, the medical area, the textile industry, the automobile industry, the construction sector, to mention a few. These discoveries, have been given thanks to the contribution of molecular biology, as well as new approaches to microscopy, which had revealed that for the biofilm formation, the biology of bacteria is involved (e.g. the interaction between bacterial cells, the physical-physical interactions. biochemistry, cell communication (QS), virulence expressions).

In the biomedical field, the biofilm formation plays an important role in when it comes to the application of materials as biomaterials (or implants), i.e. materials that interact with the human body. The importance lies in the fact that it is increasingly necessary to manufacture biomaterials that have antimicrobial properties, so that they prevent or eradicate the formation of biofilms in biomaterials, which would represent a decrease in biomaterial-associated infections, which are infections caused by bacterial adhesion and the formation of biofilms on implants.

Biomaterials have found an ally to obtain these antimicrobial properties in the use of fibers, whether of natural, synthetic or artificial origin. Micro and nano fibers play a fundamental role for applications such as: hydrogels, membranes, dressings, composites, wound dressing, and others. Usually the fibers act together with other compounds (nanoparticles, drugs) or materials, to create hybrid structures, which have a synergistic effect according to the objective for which the biomaterial is developed.

On the contrary, vegetable natural fibers, despite being a renewable resource, with low manufacturing costs, mechanical and antibacterial properties, in some cases inherent to their composition and structure, such as turmeric or bamboo, have not been used for biomedical purposes. Rather, researchers have focused on using these plant fibers as supports for bacterial immobilization, the advantage of these uses, is that one way or another has represented an advance for the study of biofilm formation on the surface of plant fibers.

The few studies about ecuadorian native fibers in the health area encourage the manufacture of composites or reinforced polymeric matrices to improve the properties of materials, according to the application field; mechanical industry, biotechnology, food, textile, biomedical. In Ecuador, the literature suggests that most approaches are reinforced materials in the construction and automobile industry, just a few approaches are for the health and biological area.

This thesis has explained the mechanisms by which bacteria are able to form biofilms, and with that structure, survive on surfaces of biomaterials that have different physicochemical, topographical and mechanical properties. These characteristics are important to a great extent, since they mediate the initial interaction of bacteria and consequently the formation of biofilms on the surfaces of biomaterials. Likewise, the importance of natural, synthetic and artificial fibers in the manufacture of biomaterials has been exposed. In addition, the main natural fibers of vegetable origin native to Ecuador have been described, and finally the interaction between biofilm and natural fibers has been elucidated.

As recommendations, it is necessary to continue research on the formation of biofilms in vegetable fibers, since it allows us to discover new techniques to apply biofilm prevention techniques, such as blocking/activating the production of autoinducers, or for the manufacture of tunable materials with surface chemical/topographical modification. Hence, natural fibers should be exploited in the biomedical field in order to produce biomaterials such as sutures, wound dressing, and composites, with the aim of take advantage of their antibacterial, mechanical, cytocompatibility, and to reduce the biomaterial-associated infection in the patient, caused by body's rejection of materials or by contamination of the surgical site.

5. BIBLIOGRAPHY

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