The Action of Phytochemicals in the Control of Pathogenic Biofilms

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Abstract The treatment of bacterial biofilms has been progressively troubled due to increasing antibiotic resistance. Biofilms exacerbate the fight against infections as they provide a protective environment for microbial cells, hindering the penetration of antimicrobial agents and favoring the uptake of elements necessary for cell survival like water, oxygen, and nutrients. Indeed, many first-line antimicrobial agents have become ineffective in treating biofilm-related infections, instigating the search for new antimicrobial agents. Natural products, particularly plant-derived compounds known as phytochemicals, have been shown to be effective, with an excellent broad-spectrum antibacterial profile, even against drug-resistant bacteria. This chapter addresses the main concepts of biofilm-associated mechanisms that promote bacterial survival. Moreover, different phytochemicals are described for biofilm prevention and control, correlating the mode of action of phytochemicals to the inhibition/alteration of virulence factors and other biofilm mechanisms. The scientific evidence of a wide variety of phytochemicals being described in this chapter should support future efforts to fast-track in vitro research to clinical applications to fight biofilm-related infectious diseases.

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1 Introduction

Since their discovery, antibiotics have been essential for the treatment and prevention of diseases, allowing many previously fatal infections to be treated or controlled (Nigam et al. 2014; Allen et al. 2019; Micoli et al. 2021). Nevertheless, the improper use and over-prescription of antibiotics, poor hygiene and sanitation habits, poor infection control, and the absence of new antibiotics led to a rapid emergence and spread of resistant microbial strains (Allen et al. 2019; Liu et al. 2021; Hawkings et al. 2007; Ferri et al. 2017; Barbieri et al. 2017). In fact, antibiotic resistance is one of the greatest threats to public health, limiting the prevention and treatment of a large range of previously treatable infectious diseases (Micoli et al. 2021; Jindal et al. 2015; Monte et al. 2014; Levy and Marshall 2004). Antimicrobial resistance (AMR) is a natural result of the adaptation of infectious pathogens to antibiotics used in a variety of fields. Moreover, the economic burden associated with these multidrug-resistant bacteria is massive (Monte et al. 2014; Prestinaci et al. 2015). Since antibiotic resistance is multifactorial, the WHO recommends a series of coordinated actions, from preventing the spread of the infection to promoting the research and development of new treatment strategies (Barbieri et al. 2017; Neu 1992; Ventola 2015). In addition, microorganisms may live in biofilms, which consist of aggregates of microbial cells attached to biotic or abiotic surfaces and embedded in a self-produced matrix of extracellular polymeric substances that protect cells from environmental stressors. It is well-known that the acquisition of resistance to antibiotics by bacteria is facilitated when they are present in biofilms (de Carvalho 2018; Yin et al. 2019; Kostakioti et al. 2013; Bridier et al. 2011). Biofilms are linked to serious and difficult-to-treat infections and combating them can be unmanageable or requires high doses of antibiotics (Llor and Bjerrum 2014; Frieri et al. 2017). Bacteria in biofilms can be up to 1000 times more tolerant to antibiotics than free-floating bacteria, which severely limits treatment options (Potera 2010; Sharma et al. 2019; Venkatesan et al. 2015).

To find novel antimicrobial agents distinct from antibiotics, plants have been explored as a source of compounds that show promising effectiveness against a variety of organisms, including fungi, yeasts, bacteria, and viruses (Monte et al. 2014; Wintola and Afolayan 2015; Cowan 1999). Phytochemicals are non-nutritive plant secondary metabolites with biological activity (Huang et al. 2016; Jimenez-Garcia et al. 2018; Liu 2013; Arendt and Zannini 2013; Diep et al. 2015). Different parts of plants from several species, such as leaves, roots, fruits, seeds, barks, stem bark, and flowers, are rich in different classes of phytochemicals, which may be a source of effective, inexpensive, and safe antimicrobial agents (Barbieri et al. 2017; Aung et al. 2020; Chouhan et al. 2017). They have been shown to inhibit peptidoglycan synthesis, destroy the structure of microbial membranes, change the hydrophobicity of bacterial membranes, and interfere with quorum sensing (QS) (Monte et al. 2014; Nazzaro et al. 2013). Plant extracts and their phytochemicals have been highlighted as promising antimicrobial agents due to their cost-effectiveness,

eco-friendliness, large structural diversity, and the possibility of reducing the resistance to antimicrobial drugs (Sakarikou et al. 2020; Giaouris and Simões 2018).

2 Biofilm-Related Infections

Biofilms are surface-related microbial structures that can be present in a large variety of environments, either abiotic or biotic (Moshynets and Spiers 2016; Balcázar et al. 2015; Lebeaux et al. 2014). One of the most important characteristics of biofilms is their capacity to ensure greater protection of bacterial cells and survive in the presence of external stressors, such as high concentrations of antimicrobials. Biofilms recalcitrance may lead to treatment failure and infection recurrence (Lebeaux et al. 2014; Aggarwal et al. 2015; Giulia and O'Toole 2021). Therefore, even in unfavorable environments, biofilms can promote the survival of pathogenic microorganisms and facilitate their spread and the recolonization of new niches (Muhammad et al. 2020; Del Pozo 2018; Roy et al. 2018; Wu et al. 2015; Kostakioti et al. 2013). Biofilms are also associated with device-related infectious diseases, which can be responsible for the development of malfunctions of devices and even chronic infections (Del Pozo 2018; Nandakumar et al. 2013; Khatoon et al. 2018). In fact, biofilms are responsible for up to 80% of human infections, such as cystic fibrosis (CFs), endocarditis, osteomyelitis, and sepsis. Thus, given the relevance of infections caused by biofilms, it is essential to highlight the pathogens considered most critical, as well as the stages of development of a biofilm, their main specific tolerance mechanisms, and their respective virulence factors.

2.1 Critical Multidrug-Resistant Pathogens

According to the WHO, certain microorganisms are particularly problematic for human health, including Gram-negative bacteria, such as *Enterobacteriaceae*, *Acinetobacter baumannii,* and *Pseudomonas aeruginosa* and ESKAPE pathogens, i.e. a group of six highly virulent, pathogenic, and antibiotic-resistant pathogens, including *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and *Enterobacter* spp. These Gram-positive and Gram-negative bacteria can evade or "escape" commonly used antibiotics due to the spread of multidrug resistance, being linked to increasing AMR infections worldwide (Santajit and Indrawattana 2016; Schultz et al. 2020; Mulani et al. 2019; Skariyachan and Garka 2018; Julian and Blumberg 2017; Karlowsky et al. 2017). Table 1 shows the main virulence factors associated with some of the most concerning bacteria, as defined by the WHO. These virulence factors are correlated with their tolerance to antimicrobial agents, as well as the development of infection in the host system.

Table 1 Main virulence factors of selected pathogens

Bacterium	Main virulence factors	References
A. baumannii	Porins; capsular polysaccharides; phospholipases; lipopolysaccharides; outer membrane vesicles; metal acquisition systems; protein secretion systems.	(Lee et al. 2017; Sarshar et al. 2021; Aliramezani et al. 2019)
P. aeruginosa	Pyocyanin; pyochelin; other pigments; elastase; phospholipase C; protease A; exotoxins and cytotoxins; flagella and pili; QS regulatory system proteins.	(Alonso et al. 2020; Britigan et al. 1992; Cox 1986)
S. aureus	Membrane-damaging toxins; toxic shock syndrome toxin; epidermolytic toxin; staphylococcal enterotoxins; pyrogenic exotoxin; exoenzymes; enterotoxin; panton-valentine Leukocidin (PVL) toxin; thermostable nuclease (TNase); adhesins; phenol-soluble modulins; surface proteins; capsular polysaccharides; invasins; surface inhibitors of phagocytosis; membrane-damaging enzymes.	(Harvey et al. 1999; Tam and Torres 2019; Dinges et al. 2000; Etter et al. 2020; Fisher et al. 2018; Balasubramanian et al. 2017; Watkins et al. 2012; Pidwill et al. 2021; Flannagan et al. 2015)
E. faecium	Proteins and carbohydrates; enzymes; enterococcal surface protein (Esp); cytolysin; cell wall adhesins efaAfm; gelatinase (gelE); aggregation substances (agg).	(Huycke et al. 1998; Mascini et al. 2006; Ike 2017; Mundy et al. 2000; Barbosa et al. 2010)

2.2 *Biofilm Formation and Specific Mechanisms*

Biofilm formation has been recognized as a multistage process. It is believed that the biofilm development process occurs through several stages, as schematized in Fig. 1.

For the successful development of a biofilm, specific mechanisms and associated virulence factors are crucial. Virulence factors are molecules produced by bacteria, which are needed to enable bacteria to attack eukaryotic cells and cause infections. They are usually encoded on mobile and integrative genetic elements, namely plasmids, bacteriophages, conjugative transposons, integrative and conjugative elements, and pathogenicity islands (Abedon et al. 2009; Sharma et al. 2017; Lami 2019; Boyd 2012). Virulence factors allow the pathogens to evade the host immune response and facilitate the establishment and long-term survival of biofilms in tissues (Zhao and Ma 2015; Phillips and Schultz 2012). Besides virulence factors, biofilms also developed several mechanisms, which are extremely important for their survival and proliferation in host tissues (summary in Table 2).

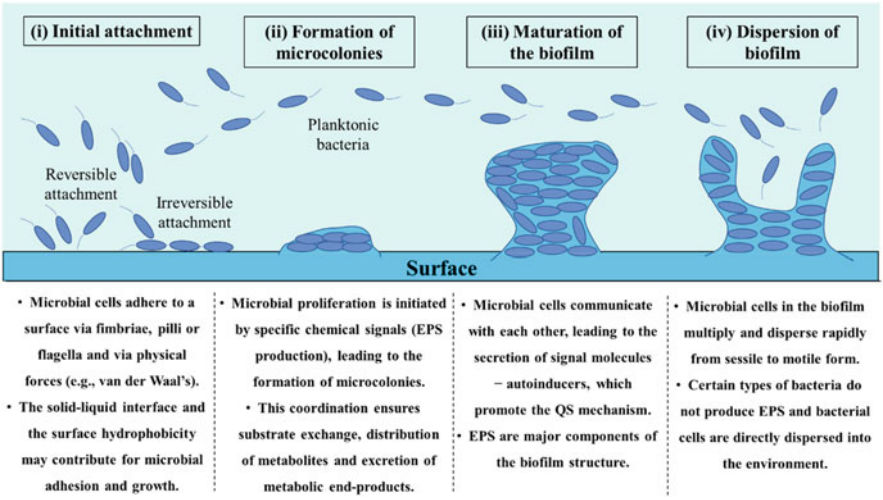

Fig. 1 Representation of the biofilm development stages (based on Jamal et al. 2018; López and Soto 2020)

3 Antibacterial Strategies Based on Natural Products to Target Biofilms

Bacterial resistance mechanisms are specific strategies of microbial evolution (Simões et al. 2009; Upmanyu et al. 2020; Ray et al. 2017). Thus, it is not surprising that new antibiotic resistance mechanisms will emerge (Barbieri et al. 2017; Diggle and Whiteley 2020; Munita and Arias 2016; Sekyere and Asante 2018). Some phenomena can explain the resistance of microorganisms to antibiotics: (i) cells can present an intrinsic and natural resistance to drugs, being "genetically programmed" to resist antibiotics (Holmes et al. 2016; Beceiro et al. 2013); (ii) microorganisms may suffer some genetic modifications like mutations, which make them insensitive to antibiotics (Fair and Tor 2014; Beceiro et al. 2013; Meredith et al. 2015); (iii) cells may become resistant to antimicrobial agents through the horizontal acquisition of genes that confer resistance to certain antibiotics from other microorganisms, which is a very extensive phenomenon and increases the probability of survival under the selective pressure caused by antibiotics (Beceiro et al. 2013; Meredith et al. 2015; Bello-López et al. 2019). Moreover, bringing a new antibiotic to the market may take up to 10 years and it is very expensive and time consuming (Barbieri et al. 2017; Spellberg 2014; Power 2006). Thus, new strategies aiming to fight bacterial infections, especially those caused by biofilms, are highly necessary (Bi et al. 2021; Srinivasan et al. 2021; Zhang et al. 2020a; Simões et al. 2009). Indeed, natural compounds, especially those obtained from plants, have become promising candidates for these much-needed treatments due to excellent antibacterial activity (Barbieri et al. 2017; Ćirić et al. 2019; Melander et al. 2020; Chassagne et al. 2021; Lahlou 2013).

Table 2 Biofilm-related mechanisms that confer bacterial protection and advantages to survive under stress conditions

	Biofilm mechanisms and their main characteristics	References
Quorum Sensing (QS)	• QS allows bacteria to communicate and modulate the expression of genes involved in bacterial survival, virulence, and pathogenicity. • The production and release of autoinducers (AIs) allow bacteria to detect changes in population density and the interaction of AIs with specific transcriptional regulators leads to population-dependent changes in gene expression. • QS systems in Gram-negative bacteria are related to a LuxI/R-like system. LuxI-type proteins are synthase proteins that catalyze the synthesis of Acyl-Homoserine Lactones (AHL) while LuxR type proteins are transcriptional activator proteins to which AHL binds, triggering transcriptional modifications. • In Gram-positive bacteria, peptides are secreted and detected by the two-component systems but can also be actively transported via ABC transporters to bind a cytoplasmic regulator.	(Floyd et al. 2017; Vattem et al. 2007; Skindersoe et al. 2008; Miller and Bassler 2001; Rutherford and Bassler 2012; Pena et al. 2019; Smith et al. 2020; Frederix et al. 2011; Harriott 2019; AL-Mamun et al. 2018; Goulden et al. 2013; Clark et al. 2019)
Adhesion	• Adhesion is the first essential step for biofilm development and it is controlled by a complex set of chemical and physical interactions. • The first adhesion process of a planktonic microorganism is reversible, and it is dictated by several physicochemical interactions, being mostly associated with van der Waals forces and electrical double layer forces (DLVO theory). • The adhesion will depend on the net sum of attractive and repulsive forces between the surfaces and the microorganism. • The second stage implies a stronger and irreversible binding of the microorganism to the surface through bacterial adhesins.	(Garrett et al. 2008; Almaguer-Flores 2013; Stones and Krachler 2016; Abraham et al. 2015; Berne et al. 2018; Meireles et al. 2015)
Motility	• Motility is one of the most dynamic bacterial phenomena, contributing to virulence through adhesion and formation of biofilms. • Six different categories of bacterial motility have been identified:	(Monte et al. 2014; Xu et al. 2014; Harshey 2003; Pollitt and Diggle 2017; Eberl et al. 1999; Tomada et al. 2016)

(continued)

Table 2 (continued)

	Biofilm mechanisms and their main characteristics	References
	Swimming, swarming, gliding, twitching, sliding, and darting. • Swimming and swarming are dependent on flagella. • Twitching and some ways of gliding require type IV pili. • Sliding/spreading are passive translocation types of motility. Information about darting is still scarce.	
EPS production	• EPS are organic polymers, namely exopolysaccharides, proteins, lipids, and DNA, crucial for the interaction between bacteria and the environment. • The extracellular matrix, composed by water and EPS, is essential for the establishment and maintenance of the structure and properties of biofilms. • The matrix stability is guaranteed by non-covalent binding between EPS involving weak physicochemical forces. • The EPS network confers cohesion and viscoelasticity to the structure.	(Costerton et al. 1999; Di Martino 2018; Jiao et al. 2010; Sheng et al. 2010; Gao et al. 2019; Flemming and Wingender 2010; Costa et al. 2018; Caro-Astorga et al. 2020; Chiba et al. 2015; Jachlewski et al. 2015)

Medicinal plants are the most abundant biological resources in traditional and modern medicine, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates, and chemical components of synthetic medicines (Desai et al. 2015; Saranraj et al. 2016; Pan et al. 2013). The intake of phytochemicals in the diet can promote health and protect the human body from diseases, being also able to reduce the risk of some chronic diseases (Jimenez-Garcia et al. 2018; Liu 2013; Yoo et al. 2018; Septembre-Malaterre et al. 2017). Phytochemicals with nutritious and healthcare properties in foods are of great significance due to their beneficial effects on human health. They are able to prevent and assist in the combat of a large variety of diseases, such as cancer, coronary heart disease, diabetes, hypertension, inflammation, microbial, viral, and parasitic infections, psychosis, spastic diseases, ulcers, osteoporosis and related diseases, among others (Thakur et al. 2020; Zhang et al. 2015; Forni et al. 2019; Guan et al. 2021; Kibe et al. 2017; Visioli et al. 2000; Howes and Simmonds 2014).

A large variety of well-known phytochemicals have been identified over the years, such as lycopene present in tomatoes, isoflavones in soybeans, and flavonoids found in fruits (Zhang et al. 2015; Ghoshal 2018; Waheed Janabi et al. 2020). An interesting feature of these compounds is their powerful antioxidant potential. In fact, the regular consumption of fruits, vegetables, and whole grains has shown to reduce the risk of various diseases related to oxidative damage, acting as free radical scavengers like hydrogen donors, electron donors, peroxide decomposers, singlet

oxygen quenchers, enzyme inhibitors, synergists, and metal chelators (Thatoi et al. 2014; Yu et al. 2021; Chen et al. 2014; Asaduzzaman 2018; Manganaris et al. 2018; Martínez et al. 2014). Phytochemicals that have significant health benefits belong to the categories of phenolic compounds, alkaloids, organosulfur compounds, phytoestrogens, terpenoids, carotenoids, limonoids, and phytosterols. All of these have shown to be highly effective in preventing and combating a wide variety of diseases (Huang et al. 2016; Jimenez-Garcia et al. 2018; Thakur et al. 2020; Singh et al. 2020; Bayir et al. 2019; Andrade et al. 2020; Koche et al. 2018; Patra 2012). Thus, the exciting properties of phytochemicals, combined with the growing need for new antimicrobial agents highlight these molecules as potential antibiofilm strategies of the future.

3.1 Targeting Bacterial Biofilms with Phytochemicals

Phytochemicals can present various mechanisms of action that have the capacity to harm the establishment and development of biofilms (Simões et al. 2009). These mechanisms include the inhibition of peptidoglycan synthesis (Monte et al. 2014; Nazzaro et al. 2013), cytoplasmatic membranes and cell wall damage and disruption (Suarez et al. 2005; Oussalah et al. 2006; Haraguchi et al. 1996), modification of hydrophobicity and permeabilization of the bacterial membranes (Cox et al. 2000; Carson et al. 2002; Trombetta et al. 2005; Melzig et al. 2001; Ultee et al. 1999), efflux pump inhibition (Aeschlimann et al. 1999; Schmitz et al. 1998; Khan et al. 2006; Micol et al. 2001), inhibition of RNA or DNA synthesis (Mori et al. 1987; Cushnie and Lamb 2005; Feldberg et al. 1988; Sundar and Chang 1992), inhibition/interference of enzyme activity and of the electron transport chain (Lin et al. 2005; Mirzoeva et al. 1997; Sinha Babu et al. 1997; Mandal et al. 2005). Despite the wide variety of phytochemical molecules that have been described as bioactive and of potential interest as food supplement or drug, only few were approved by the US Food and Drug Administration (FDA) (Kongkham et al. 2020).

Phytochemicals with antibiofilm properties include, for example, quercetin, which can inhibit the production of alginate, leading to a decrease in the adhesion during the biofilm development (Górniak et al. 2019; Memariani et al. 2019; Lee et al. 2013). Another example is (+)-usnic acid, which has been used to modify polyurethane surfaces to evaluate its influence on the development of *S. aureus* and *P. aeruginosa* biofilms (Francolini et al. 2004). The results showed that the formation of *S. aureus* biofilms for a period of up to 6 days was inhibited on polyurethane surfaces with (+)-usnic acid. On the contrary, *P. aeruginosa* biofilms were able to develop on surfaces of (+)-usnic acid-treated polymer. In fact, the (+)-usnic acid has higher antimicrobial activity against *S. aureus* than against *P. aeruginosa,* as translated by the minimum inhibitory concentration (MIC), which was 32 μg/mL for *S. aureus* and 256 μg/mL for *P. aeruginosa.* (+)-usnic acid was also able to affect the morphology of *P. aeruginosa* biofilms, since the biofilm was thinner and flat in the control polymer and in the (+)-usnic acid-treated polymer the biofilm was

substantially thicker and rougher (Francolini et al. 2004). Another phytochemical that exhibited very interesting results is emodin, which inhibited the development of biofilms by *P. aeruginosa*, *E. coli, and S. aureus* through the decrease of expression of key genes involved in biofilm formation. Moreover, several studies also evaluated the effect of plant extracts on biofilm control, instead of pure and isolated phytochemicals. The use of extracts containing different molecules may result in synergistic interactions, which may explain the positive results obtained with low doses of active compounds in herbal products. This highlights the hypothesis that the use of plant extracts may be advantageous in comparison with the use of single phytochemicals (Borges et al. 2016).

The effectiveness of phytochemicals and plant extracts in combating infections may be justified by alterations caused in specific biofilm mechanisms, as described in the following sections.

3.1.1 Effects of Phytochemicals in QS Mechanisms

QS is a crucial regulatory mechanism involved in biofilm formation and differentiation (Borges et al. 2014a). It allows bacteria to communicate through the delivery and sensing of small signal molecules, ensuring relevant advantages for bacteria in regard to colonization, biofilm development, defense, adaptation, virulence, and pathogenicity (Rutherford and Bassler 2012; Pena et al. 2019; Li and Tian 2012; Grainha et al. 2020). Therefore, studying natural molecules with the ability to interfere with QS and understanding their effects may be an important way to fight bacterial tolerance and biofilms (Rutherford and Bassler 2012; Borges et al. 2014a; Lade et al. 2014). In fact, several studies have shown the action of specific phytochemicals on QS and consequently the possibility to retard or avoid biofilm development. For instance, the synthetic halogenated furanone, a secondary metabolite compound derived from furanone present in the Australian macroalgae *Delisea pulchra*, has shown great potential in affecting the bacterial signaling QS, as well as the motility of cells. Based on the structural similarity between *D. pulchra* furanone and Acyl-homoserine lactone (AHL) molecules, it is hypothesized that this furanone may be responsible for interfering with the interaction of the putative regulatory protein and AHL molecule through its competitive binding to the receptor. Moreover, furanones can also inhibit surface aggregation traits, when in an ecologically significant concentration (Roy et al. 2018). Hentzer et al. suggested that rhl system, which is a QS mechanism in *P. aeruginosa*, is a target to furanone (Hentzer et al. 2002). This compound can penetrate the biofilm matrix of *P. aeruginosa*, interfering with genes related to QS biofilm maturity expression. Hence, this compound is capable of changing the biofilm structure, which promotes the detachment of bacteria and leads to the loss of bacterial biomass in the matrix, also mediating the displacement of AHL molecules from LuxR receptor sites (Roy et al. 2018; Hentzer et al. 2002; Hentzer and Givskov 2003; Asfour 2018; Alasil et al. 2015).

Certain polyphenol compounds, such as epigallocatechin gallate (EGCG), tannic acid, ellagic acid, gallic acid, and ferulic acid are also promising molecules for inhibiting biofilm development. Some studies linked the antibiofilm activity of these polyphenolic molecules to the interference in QS. For instance, Huber et al. demonstrated that polyphenolic compounds, such as gallic acid, (−)-epigallocatechin gallate, (+)-catechin and tannic acid were capable of interfering with QS mechanisms of *E. coli* and *P. putida* through the blockade of the AHL system (Quave et al. 2012; Huber et al. 2003). Quercetin, as well as some others flavonoids, have also shown to be efficient in affecting the QS mechanisms of several microorganisms, such as *P. aeruginosa*, *S. aureus*, *Escherichia coli*, *Enterococcus faecalis,* and *Streptococcus mutans*.

Curcumin, from the rhizome of *Curcuma longa*, showed strong and effective biofilm inhibitory activity related to the regulation of the expression of genes involved in QS and associated with the production of alginate and exopolysaccharides. Curcumin has also shown effects in inhibiting the swimming and swarming motilities and increasing biofilm susceptibility to antibiotics (Borges et al. 2016; Packiavathy et al. 2013; Packiavathy et al. 2014). A study performed by Kali et al. demonstrated that curcumin in combination with ciprofloxacin was effective against biofilms of Gram-positive bacteria. Moreover, this compound was also effective against Gram-negative biofilms when combined with the antibiotics amikacin, gentamicin (GEN), and cefepime. These results revealed the potential of using curcumin in a combination therapy (Kali et al. 2016). In addition, emodin induced the proteolysis of *E. coli* QS signal receptor TraR and enhanced the activity of ampicillin against *P. aeruginosa. This compound* has also been associated with the downregulation of the *cidA* gene, which is involved in cell lysis and eDNA release (Borges et al. 2016; Yan et al. 2017; Harapanahalli et al. 2015; Zhang et al. 2020b).

Regarding the use of plant extracts, Zhang et al. evaluated the antibiofilm and QS inhibition activity of an extract from *Rosa rugosa* tea, whose main components are polyphenols and flavonoids (Zhang et al. 2014). This extract inhibited the production of violacein, controlled by QS in *C. violaceum*. Furthermore, this extract also inhibited the biofilm formation by *E. coli* and *P. aeruginosa, which may be related not only to its quorum quenching activity, but also to the inhibition of bacteria swarming motility*. Glycosyl flavonoids, such as chlorogenic acid, isoorientin, orientin, isovitexin, vitexin, and rutin were also capable of inhibiting the QS in *C. violaceum* and *E. coli*. Moreover, there are more plant components with QS inhibition properties, such as extracts from liverwort *Lepidozia chordulifera, where it is possible to find* sesquiterpenoid viridiflorol, triterpenoids, ursolic and betulinic acids (Zhang et al. 2014). Other relevant and efficient phytochemicals with antiquorum sensing effects include N-(heptylsulfanylacetyl)-L-homoserine lactone, extracted from garlic (able to interrupt QS signaling by competitively inhibiting transcriptional regulators LuxR and LasR), limonoids, and hordenine (Klančnik et al. 2021). Furthermore, baicalin hydrate, cinnamaldehyde, and hamamelitannin have been shown to significantly improve the susceptibility of *P. aeruginosa*, *B. cenocepacia,* and *S. aureus* biofilms, including MRSA, in combination with

conventional antibiotics. In fact, hamamelitannin can act as a QS inhibitor by increasing both the in vitro and in vivo susceptibility of MRSA biofilms, which can be associated with its ability to interact with the TraP receptor and affect the release of eDNA (Brackman et al. 2011; Yuan et al. 2020; Jiang et al. 2019).

There are more examples of studies that equally show promising results of phytochemicals regarding antiquorum sensing activity. It was demonstrated by Niu et al. that *Cinnamomum cassia* extract, containing cinnamaldehyde and eugenol, significantly inhibited QS of *E. coli* and *Vibrio harveyi* (Niu et al. 2006). In addition, clove, cinnamon, peppermint, and lavender also exhibited antiquorum sensing activity, according to Khan et al. (Khan et al. 2009). Iberin, which is an isothiocyanate and sulfoxide, interfered with the QS mechanism of *P. aeruginosa* and induced apoptosis. Organosulfur compounds from garlic, such as allicin and ajoene, were able to inhibit QS of *P. aeruginosa* and *E. coli* (Borges et al. 2013). In another study by Vikram et al. flavonoids were evaluated for their capacity to interfere with QS of *V. harveyi* and inhibited the development of *E. coli* O157:H7 and *V. harveyi* biofilms (Vikram et al. 2010). The results showed that kaempferol, naringenin, quercetin, and apigenin were able to act as nonspecific inhibitors of autoinducer-mediated cell–cell signaling processes. In addition, these molecules inhibited the formation of *V. harveyi* and *E. coli* O157:H7 biofilms (Vikram et al. 2010).

3.1.2 Effects of Phytochemicals on Motility

Motility, which generally depends on flagella and pili, is one of the crucial factors that contribute to biofilm formation and development, especially at an earlier stage, since these mechanisms require a multicellular movement and dispersion on a surface (Monte et al. 2014; Lemon et al. 2007; Cai et al. 2020; Kearns 2010; Köhler et al. 2000). It has been already shown that many natural compounds, extracts or pure products, have the capacity to interfere with the bacterial motility of several microorganisms (Vattem et al. 2007; Liaqat et al. 2018), which may be reflected on the reduction of biofilm formation ability. Swimming and swarming motilities of *P. aeruginosa*, *Proteus mirabilis,* and *Serratia marcescens* were inhibited by methanolic extracts of *Cuminum cyminum*, especially methyl eugenol, a compound with a well-studied antibiofilm activity. In addition, cinnamaldehyde and eugenol, from *Cinnamomum cassia*, were able to compromise the development of *E. coli* biofilms by interfering with their swimming motility (Monte et al. 2014). Gallic acid and ferulic acid displayed potential to inhibit the motility and adhesion of four pathogenic bacteria, including *E. coli*, *P. aeruginosa*, *S. aureus,* and *Listeria monocytogenes*. Identical results were obtained for isothiocyanates allyl isothiocyanate (AITC) and 2-phenylethyl isothiocyanate (PEITC) (Borges et al. 2012). Ferulic acid and salicylic acid (SA) were reported to inhibit swimming motility of *Bacillus cereus* and *Pseudomonas fluorescens (*Lemos et al. 2014*)*.

Camellia nitidissima Chi is a well-known edible plant from China with diverse biological and medicinal properties, especially antibacterial activity. A study

performed by Yang et al. assessed the inhibitory activity of the dichloromethane fraction (DF) of *C. nitidissima* Chi flowers on the pyocyanin production, as well as on the swarming and swimming motility of *P. aeruginosa* PAO1, at sub-minimum inhibitory concentrations (Yang et al. 2018). DF was associated with a concentration-dependent inhibition activity in relation to swarming and swimming motility. Moreover, the half maximal inhibitory concentrations (IC50) were determined and they found values of 0.158 ± 0.009 mg/mL for pyocyanin production, 0.139 ± 0.004 mg/mL for swarming motility, and 0.334 ± 0.049 mg/mL for swimming motility. In addition, the results of a real-time polymerase chain reaction (RT-PCR) showed that DF significantly downregulated the expression of rhlR and lasR (Yang et al. 2018). In fact, *las* and *rhl* systems are the two principal QS mechanism elements of *P. aeruginosa.* Finally, through the high-performance liquid chromatography (HPLC)-triple-time of flight (TOF)-MS/MS analysis, it was found that DF is mainly composed of gallic acid, catechin, ellagic acid, chlorogenic acid, quercetin, and kaempferol. These six identified compounds displayed inhibitory effects on pyocyanin production, swarming, and swimming motilities. Ellagic acid showed the strongest effect with IC50 values of 0.067 ± 0.002 mg/mL for pyocyanin production, 0.024 ± 0.008 mg/mL for swarming motility, and 0.020 ± 0.003 mg/mL for swimming motility (Yang et al. 2018). Therefore, it is possible to infer that all these alterations caused by DF may cause significant effects on the ability of *P. aeruginosa* to form biofilms.

In another study by Borges et al., the effect of AITC and PEITC on planktonic cell susceptibility, bacterial motility and adhesion, and biofilms of *E. coli*, *P. aeruginosa*, *S. aureus,* and *L. monocytogenes* was evaluated (Borges et al. 2014b). AITC caused complete inhibition of swimming motility of *P. aeruginosa* and total inhibition of swarming motility of *E. coli*, while PEITC caused complete inhibition of swimming motility of *E. coli*, *P. aeruginosa,* and *L. monocytogenes* and swarming motility of *E. coli* and *P. aeruginosa*. Moreover, the spreading motility of *S. aureus* was completely inhibited by PEITC. AITC and PEITC presented a preventive effect on biofilm formation, which may be related to the effects on the inhibition of bacterial motility. Moreover, AITC and PEITC showed a high potential to reduce the mass of biofilm formed by the Gram-negative bacteria (Borges et al. 2014b).

3.1.3 Effects of Phytochemicals on Adhesion

Bacterial adhesion to the surface of materials is the first step that leads to the formation of a biofilm and, from the moment the adhesion occurs, it is possible for the bacteria to communicate with each other and establish a community (Klančnik et al. 2021; Dunne 2002; Flemming et al. 2016). Therefore, since bacterial adhesion to a surface is an initial prerequisite for biofilm formation, it is essential to identify natural compounds capable of interfering with this phenomenon, which may constitute an important target when developing strategies for controlling pathogenicity (Kostakioti et al. 2013; Verderosa et al. 2019). Within this context, phenolic

compounds have been shown to exhibit important roles in preventing bacterial adhesion, including the adhesion of *Campylobacter jejuni* (Klančnik et al. 2021). In a study of Pogačar et al., thyme ethanolic extract (TE), thyme post-hydrodistillation residue (TE-R), and olive leaf extract (OE) were evaluated for their phytochemical composition using high-performance liquid chromatography (HPLC) with photodiode array, and antimicrobial activity against *C. jejuni* (Šikić Pogačar et al. 2016). The analysis showed that the main components present in TE and TE-R were flavone glucuronides and rosmarinic acid derivatives, while in OE verbascoside, luteolin 7-O-glucoside and oleuroside were the major compounds. The compounds TE and TE-R were able to decrease *C. jejuni* adhesion to the abiotic surface by up to 35%, at a concentration range between 50–200 μg/mL, and up to 30%, at a concentration range between 0.2–12.5 μg/mL. TE-R was more effective than TE and displayed a meaningful inhibition of *C. jejuni* adhesion (higher than 30%), reaching up to 40%. When considering a concentration range of OE between 3.125–12.5 μg/mL, biofilm formation was affected and the adhesion inhibition reached 10% to 23%, respectively. In addition, the anti-adhesion effect of *C. jejuni* to cell cultures was also assessed and it was observed that the *C. jejuni* adhesion toward pig small intestine epithelial cell line, PSI cl1 cells, was remarkably decreased up to 30% in the presence of TE, TE-R, and OE at a concentration range between 0.78–200 μg/mL (Šikić Pogačar et al. 2016).

The North American cranberry is also recognized for its high levels of phytochemicals, including phenolic acids, flavonoids, and ellagic acid (Walton 2014). The antimicrobial properties of cranberry species have been associated with high levels of polyphenol compounds, particularly proanthocyanidin (PACs). So far, several data have revealed that PACs have unique characteristics that allow the inhibition of bacterial adhesion to epithelial cells. Indeed, the studies developed by various authors have shown that there is a direct correlation between the ingestion of cranberries and the prevention of urinary tract infections (UTIs) in females (Walton 2014; Kontiokari et al. 2005; Carson and Riley 2003; Tempera et al. 2010). Several in vitro studies have already been performed and demonstrated that the anti-adhesion effects of PACs are responsible for a reduction in the bacterial adherence to urinary tract cells such as uroepithelial cells, but also to other biological materials (Walton 2014; Kontiokari et al. 2005). Furthermore, cranberry extracts also seem to have similar inhibitory effects on tissue adhesion with regard to Gram-negative bacteria, including the ones of the genera *Proteus*, *Klebsiella*, *Enterobacter,* and *Pseudomonas*. The intake of cranberry has been associated with a decrease in the incidence of gastric ulcer and gastric cancer (Walton 2014). Burger et al. showed that for cultured gastric epithelial cells, the phytochemicals found in cranberry juice can specifically interfere with a sialyllactose-specific adhesion mechanism that allows *Helicobacter pylori* to adhere to the gastric mucosa. Consequently, these authors inferred that the cranberry juice could also inhibit the adhesion of bacteria to the stomach in vivo and acting in the prevention of stomach ulcers that are caused by *H. pylori*. (Walton 2014; Burger et al. 2002).

Phenolic and polyphenolic compounds have also been shown to have substantial anti-adhesion effects. A work performed by Toivanen et al. evaluated the

anti-adhesion activity of different molecular size fractions of wild cranberry *Vaccinium oxycoccos* polyphenols against *Streptococcus pneumoniae* and *Streptococcus agalactiae* (Toivanen et al. 2010). Moreover, according to Borges et al., there are other phytochemicals with very impressive anti-adhesion activity, namely cinnamaldehyde and eugenol, from *Cinnamomum cassia*, which interfered with adhesion and biofilm formation of *E. coli* (Borges et al. 2013). Polyanacardic acid, polysalicylic acid, catechin, epigallocatechin, and tannic acid also exhibited anti-adhesion activity and inhibited the formation of *Streptococcus mutans* and *P. aeruginosa* biofilms (Borges et al. 2013). In another work of Lee et al., the potential effects of phloretin, which can be found, for instance, in apples, were investigated (Lee et al. 2011). Phloretin reduced the attachment of *E. coli* O157:H7 to human colon epithelial cells and decreased the formation of *E. coli* O157:H7 biofilms. It was also demonstrated that phloretin was able to repress genes associated with toxicity, hlyE and stx(2); the autoinducer-2 importer genes, lsrACDBF; curli genes csgA and csgB; and also prophage genes of *E. coli* O157:H7 biofilms (Lee et al. 2011).

3.1.4 Effects of Phytochemicals on the EPS Production

EPS have a wide range of biological functions, being part of the carbon and energy reserves, preventing desiccation, protecting against environmental stresses, providing protection against toxins and antibiotics, as well as playing a crucial role in pathogenicity, symbiosis phenomena, and adhesion to surfaces (Singha 2012; Whitfield et al. 1993; Roberts 1996; Khan and Iqbal 2017). Hence, it is fundamental to discover and understand the role of natural compounds in inhibiting the production of EPS with regard to controlling and fighting biofilms (Mishra et al. 2020; Koo et al. 2017). Several studies described significant action of extracts and specific phytochemicals on EPS inhibition and removal. For instance, Borges et al showed that methyl eugenol interfered with EPS production (Borges et al. 2013). In a study developed by Packiavathy et al., the inhibitory properties of spices and vegetables, commonly found in South India, on the QS and EPS production of the bacteria *C. violaceum* were evaluated (Packiavathy et al. 2012). In the 22 samples tested, the QS inhibitory compound present in the methanolic extract of *Cuminum cyminum*, at a concentration of 2 mg/mL, was able to inhibit the production of violacein by *C. violaceum*. In addition, it was demonstrated that the *C. cyminum* extract highly interfered with the physiological functions regulated by AHL and the formation of biofilms, including flagellar movement and EPS production. The QS inhibitory effects shown by this plant were assigned to methyl eugenol, considering the results of molecular docking analysis. At a sub-MIC level, it promoted damage to the biofilm structure and strongly inhibited the biofilm formation of *P. aeruginosa* PAO1, *P. mirabilis,* and *Serratia marcescens* (Packiavathy et al. 2012). Abraham et al. assessed the inhibition of EPS production by methanolic fraction of the dried fruits of *Caesalpinia spinosa.* Also, the ability to inhibit biofilm formation by *E. coli*, *P. mirabilis*, *S. marcescens,* and *P. aeruginosa* PAO1 was assessed (Issac Abraham

et al. 2011). In addition, its effect in inhibiting QS-dependent phenomena, such as violacein production in *C. violaceum* and swimming and swarming motility was also investigated. It was observed that the extract of *C. spinosa* interfered with swimming and swarming motility, EPS production and biofilm formation in *E. coli*, *P. mirabilis*, *S. marcescens,* and *P. aeruginosa* PAO1. Here, the extract revealed a strong QS inhibition effect, in a concentration-dependent way, however, without interfering with the microbial growth. At a concentration of 2 mg/mL, this extract significantly restricted the EPS production to 58, 46, 66, and 67%, as well as limited biofilm formation to 79, 75, 73, 70%, in *S. marcescens*, *P. aeruginosa* PAO1, *E. coli,* and *P. mirabilis*, respectively (Issac Abraham et al. 2011).

There are other phytochemicals with a proven ability to inhibit EPS production. A well-known compound is (−)-epigallocatechin gallate (EGCg), which has several antimicrobial action modes, including the ability to decrease EPS production (Borges et al. 2013). EGCg is the major component of tea catechins and displayed an inhibitory effect, EPS degradation capacity, and a destructive action against *E. coli* biofilms (Maeyama et al. 2005). Taking into account the EGCg effects, Maeyama et al. developed a new bactericidal surface based on a catechin polymer (Maeyama et al. 2005). The surfaces tested, containing EGCg, were prepared through photopolymerization of liquid biodegradable polyesters and the rate of releasing was potentiated by increasing the rate of surface-erosion of the polymers. Interestingly, polymers exhibiting a higher releasing ability showed a lower biofilm development on the surfaces. Moreover, EGCg induced a biofilm-destructing effect, such as EPS degradation, damage of bacterial membrane, and cell detachment (Maeyama et al. 2005). Allicin is another phytochemical with remarkable proven evidence in relation to EPS production. Lihua et al. investigated the activity of allicin against *P. aeruginosa* biofilm development, specifically their effect on the production of virulence factors controlling the QS mechanism and EPS (Lihua et al. 2013). The authors found that the EPS production increased over time, but decreased with the concentration of allicin used in the treatment. The study also demonstrated that although the dry weight of bacteria between the different groups was almost equal to the one registered at the beginning of the experiments, the total amount of EPS was significantly reduced when allicin was used. Moreover, bacterial adhesion was significantly reduced compared to the saline control group, when 128 μg/mL of allicin was used. Interestingly, when the biofilm was treated with 10 μg/mL of allicin, it became thinner, and its structure was compromised. Similar results were obtained for the group treated with 128 μg/mL of allicin, in which the biofilm thickness was reduced from 28.83 μm to 16.50 μm. The effect of allicin on the virulence factors exotoxin A, elastase, pyoverdine, and rhamnolipid was also assessed, being demonstrated that allicin significantly downregulated the expression of exotoxin A and elastase. In addition, there was a complete inhibition of rhamnolipid and pyoverdine production. Thus, allicin can affect the development and maturation of *P. aeruginosa* biofilms, suggesting that this compound may be a promising therapy for treating bacterial biofilms (Lihua et al. 2013).

4 Conclusions and Future Perspectives

Antibiotic resistance is a serious problem in modern society. It has been claimed for many years that several natural plant products have medicinal effects, which make them promising for the treatment of various diseases. The development of natural, safe, and effective therapies helps control and minimize antibiotic resistance. Within the broad therapeutic and nutritional effects of phytochemicals, the ability to impair biofilm mechanisms, damage the bacterial membrane, restrict biofilm formation and silence virulence factors make them highly sought-after, effective antimicrobial agents. Besides the interference of phytochemicals with many planktonic bacterial processes, these natural compounds also have promising antimicrobial effects on biofilm mechanisms, such as adhesion, motility, QS and EPS production, displaying a strong activity against virulence factors of both planktonic and sessile cells. Nevertheless, further research is needed to develop and tailor specific applications of phytochemicals for therapeutic and clinical purposes, to assess their safety profile, to confirm their efficacy in vivo and in humans, and to ensure appropriate and selected use to prevent the future emergence of resistances.

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