Biofilm prevention and control by dietary phytochemicals

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Antimicrobial resistance is a major public health concern, particularly in hospitals and other health care settings, and have increased worldwide. The evolution of resistance can be attributed to the selective pressure caused by the indiscriminate use of antibiotics and the transmission of resistance within and between individuals. Nowadays, some infectious diseases are almost untreatable by conventional antibiotic therapy. In most of the cases, the limited efficacy of antibiotics in the treatment of infections is related to biofilm formation. It is estimated that biofilms contribute to over 80% of all infections in humans. Bacteria in sessile state are more protected against host defences and more resistant to antimicrobial treatment than their planktonic counterparts. So, new antimicrobial products and strategies are required in order to more effectively control biofilms. Plants synthesize several secondary metabolites (phytochemicals) that are recognized as fundamental source of chemical diversity and are important pharmaceutical products. In the last few years, several classes of phytochemicals have shown to have antimicrobial properties against clinical important pathogenic microorganisms, and capacity to reduce the risk of various diseases. This chapter aims to review the importance and possible use of dietary phytochemicals for biofilm prevention and control, through the interference with some factors that are involved in biofilm development, particularly motility, adhesion and quorum-sensing (QS).

Keywords antibacterial activity; biofilm prevention/control; dietary phytochemicals; pathogenic bacteria; resistance

1. Antimicrobial resistance and biofilms

The resistance of microorganisms to multi-drugs is a global public health problem, not only within healthcare institutions, but also in communities and other sectors such as food industry. During the last years, due to the increase of pathogens resistance, the current antimicrobial agents are losing their efficiency, and some infectious diseases are almost untreatable [1, 2]. This problem can be due to the selective pressure caused by the indiscriminate use of antibiotics, inadequate therapeutic strategies and the transmission of resistance within and between individuals [3-6]. Another drawback of the use of conventional antimicrobials is their failure to treat infections caused by bacteria, when they form biofilms [7-9].

Biofilms comprise sessile microbial communities surrounded by a matrix of extracellular polymeric substances (EPS), such as proteins, nucleic acids and polysaccharides [10, 11]. This bacterial phenotype is an example of physiological adaptation, which is more difficult to eliminate, and is one of the most important sources of recalcitrant infections [12]. Biofilms are commonly associated with many health problems (e.g. periodontal disease, endocarditis, osteomyelitis, cystic fibrosis, infections related to surgical implants) [12-14]. Over 80% of bacterial infections in humans involve the formation of biofilms [13, 15]. Bacteria embedded in biofilms are less susceptible to host defences and more resistant to antimicrobial products (10-1000 times) than their planktonic counterparts [9, 16, 17]. This enhanced resistance can be correlated to the fact that planktonic and sessile cells differ considerably in their physiology, gene expression and morphology. The conventional mechanisms of antibiotic resistance, such as efflux pumps, modifying enzymes, and target mutations, do not seem to be the only responsible for the protection of bacteria in biofilms [16]. The mechanisms of resistance in bacterial biofilms are beginning to be elucidated [9]. Possible explanations for the improved resistance of bacteria in biofilm comprise: (i) poor penetration or inactivation of antimicrobials in the extracellular polymeric matrix; (ii) outer membrane structure; (iii) an altered bacterial metabolic state; (iv) the presence of persister cells; (v) genetic adaptation; (vi) resistance induced by the antimicrobial itself following the use of sublethal concentrations and the upregulation of efflux pumps [7, 18].

Biofilm resistance is commonly multifactorial and can vary from one organism to another [19]. Treatment of infections associated to biofilms with existing approved therapies remains a significant medical challenge. Moreover, the eradication of biofilms with single target antimicrobials is difficult to perform, and combination of distinct bacterial targets is needed for treating biofilm infections. Therefore, the ability of sessile bacteria to resist antimicrobial agents clearly shows that new control approaches are required [20, 21]. An important strategy to fight the resistance problem involves the search of novel antimicrobials capable of suppressing bacterial resistance mechanisms, or of working in synergy with the currently available antimicrobial agents. The use of compounds with different targets in the cell of pathogenic bacteria in this mode of growth is another possible mechanism [1, 22, 23]. This has led to an increased interest in natural antibacterial products, which can restrict the ability of bacteria to adhere, communicate, and form

complex biofilms [24]. In fact, motility, adherence and biofilm formation are from the primary steps in bacterial pathogenesis and in the development of antimicrobial resistance [25].

2. Biofilm development

Biofilm formation is a dynamic and multicellular process that involves a series of steps, namely: (1) preconditioning of the adhesion surface either by macromolecules present in the surrounding environment or intentionally coated on the adhesion surface; (2) transport of planktonic cells from the surrounding medium to the surface; (3) adsorption of cells at the surface for a finite time; (4) release of reversibly adsorbed cells; (5) irreversible adsorption of bacterial cells at a surface; (6) production of cell-cell signaling molecules; (7) transport of substrates to and within the biofilm; (8) substrate metabolism by the biofilm-bound cells and transport of products out of the biofilm and (9) biofilm removal by detachment or sloughing [12, 26]. So, biofilm formation is a developmental process mediated by a combination of adhesion mechanisms, bacterial motility and quorum-sensing (QS) phenomenon. The best strategy for biofilms control or eradication is the prevention of their development. Therefore, the cellular processes of biofilm formation, maintenance, and dispersal are important targets for the discovery of new drugs [23].

Motility is arguably one of the most impressive features in microbial physiology. Six different types of motility have been identified, swimming, swarming, gliding, twitching, sliding and darting [27]. Bacteria use flagella for swimming, swarming and darting motilities. These can contribute to the virulence of pathogens through adhesion and biofilm formation on biotic and abiotic surfaces. Swarming motility has long been recognized as a bacterial social behavior and has been shown to be important for both initial interaction with the surface and for movement along it [21, 28, 29]. Twitching has been shown to require type IV pili. Gliding and sliding are surface movements that do not require flagella or pili [27, 30]. Motile cell senses stimulates and alter the functioning of its motility machinery to improve its chances of migrating to a better location [31]. Bacteria in a motile state suffer alterations in their morphology which distinguish them from their planktonic state [32]. Increased resistance of motile bacteria compared with their planktonic counterparts was also observed [33]. Motility seems to be critical for transition from planktonic to surface-associated life-style [34]. For this reason, motility inhibition can be correlated with a decreased ability of bacteria to form biofilms. Shrout et al. [35] demonstrated that differences in surface motility could explain differences in biofilm structure at early stages of development. Therefore, the inhibition of bacterial motility can represent an important strategy to control biofilms.

In addition to motility, it is necessary to understand other factors that are involved in biofilm development, such as the initial adhesion process. Bacterial adhesion to surfaces has been studied extensively over the past decades in many diverse areas [25, 36]. Adhesion is a complex process that is affected by many factors including the physicochemical characteristics of bacteria (hydrophobic interactions), the material surface properties, and the environmental factors. The biological properties of bacteria, such as the presence of fimbriae and flagella and the production of EPS, also influence the attachment to surfaces [37, 38]. Microbial adhesion and biofilm formation are the main concerns in the control of infection associated to biofilms.

Another important event related to bacterial biofilm growth and differentiation is QS [39]. QS is a form of cell-to-cell interaction in bacteria mediated by production of signaling molecules called autoinducers (AIs), in response to the increase in cell density [40, 41]. There are several classes of AIs, based on common molecular features. These include acyl homoserine lactones (AHLs), autoinducing peptides (AIPs) and autoinducer-2 (AI-2). Gram-positive bacteria are mediated by AIPs, and Gram-negative predominantly employ AHLs as AIs. AI-2 is involved in inter-specific communication in both Gram-negative and positive bacteria [42, 43]. AHLs are the best characterized molecules. This system of intercellular communication regulates several physiological functions in many Gram-negative bacteria, such as: bioluminescence, pigment and antibiotic production, and exopolysaccharide synthesis [44, 45]. In addition, it has been shown that QS is an important regulatory mechanism in the expression of genes involved in processes related to survival, virulence and pathogenicity [23, 41, 46]. Various pathogenic bacteria such as *Pseudomonas aeruginosa*, *Vibrio* sp., *Burkholderia cepacia* and *Yersinia enterocolitica* employed QS to regulate their virulence and pathogenicity [47]. The interference with this system of communication can affect biofilm formation/maturation and make the bacteria more susceptible to antimicrobials [23, 48].

QS inhibitors are a possible key to overtake the deficiencies associated with the use of traditional antibiotics to treat infections caused by bacterial biofilms [49]. Compounds with a structure similar to the natural AIs (such as furanones) or synthesized derivatives are a good option for QSI. Due to their similarity, these compounds can bind to the cells instead of AHLs. However, these compounds have limitations for human use due to their toxicity, carcinogenic properties and instability under aqueous conditions [46].

The recognition of biofilm formation as a multicellular developmental process is important because this perception will permit the application of new approaches for the treatment of persistent infections in biofilms.

3. Natural products to prevent and control biofilm formation

In recent years, drug resistance of human pathogenic bacteria has been extensively reported. Moreover, persistent infections were also observed due to improved resistance of bacteria in biofilm [50, 51]. This creates a tremendous economic loss and pressure on the medical community to find alternative approaches for the treatment of diseases related with biofilms. Therefore, efforts are been applied to discover efficient antimicrobial molecules not so vulnerable as current drugs to bacterial resistance mechanisms, including those in biofilms [1, 52]. Some natural products have distinctive properties that make them perfect candidates for these much needed therapeutics [26].

Plants produce an enormous array of secondary metabolites (phytochemicals) that are not essential for their normal physiological functions. However, these bioactive compounds are used to protect plants against attacks of microorganisms, herbivores, insects, nematodes and even other plants [53, 54]. The importance of diverse natural product has been recognized by humans due to their beneficial properties for health. Inclusively, many classes of plant secondary metabolites have demonstrated their potential as antimicrobials or synergists of other products [55, 56]. So, nowadays phytochemicals are a fundamental source of chemical diversity and important components of the current pharmaceutical products [1, 54, 55, 57].

3.1. Dietary phytochemicals

As mentioned, many of the antimicrobial drugs used to effectively treat human diseases have been derived from nature [58]. The interest in antimicrobials derived from natural sources has increased in the last years due to the fact that many antibiotics had become ineffective in the treatment of microbial infections. The accepted safe status of some of these compounds, associated with lower adverse effects and reduced cost compared with folk pharmaceuticals was also an encouraging factor [59, 60]. However, the attention in natural products is not new. On the contrary, this interest remains for centuries with the use of plant extract for the treatment of some diseases, in traditional medicine. In this context it is known that some dietary phytochemicals, such as essential oils (EO), phenolics, glucosinolates (GLS) and their hydrolysis products, have a wide range of effects for health, preventing the risk of some diseases [56, 61, 62]. These properties include antibacterial, antiviral, antioxidant, anti-inflammatory, antiallergic and anticarcinogenic activities, hepatoprotective and antithrombotic effects, and vasodilatory action [55, 63-71].

Currently, several researchers were able to identify improved strategies for biofilm control. Thus, considering the numerous therapeutic properties of dietary phytochemicals, and the fact that these compounds are thought to be an integral part of both human and animal diets, it is important to study their activity against bacterial biofilms. In fact, as previously demonstrated by some authors, phytochemicals could represent a natural antimicrobial strategy with significant impact not only against planktonic bacteria but also on bacterial biofilm formation and development. Following, we will review and highlight some studies about the possible use of dietary phytochemicals for biofilm prevention and control, and their interference with motility, adhesion and QS (Table 1).

3.1.1. Essential oils

EO are complex mixtures of volatile compounds with strong odor that are synthesized in several plant organs. These volatile compounds play an important role in the protection of plants, against microorganisms [71]. Terpenoids (monoterpenoids and sesquiterpenoids) and phenylpropanoid are the two principal classes of EO, where the terpenoids are the more diversified group of plant bioactives found in many herbs and spices. The biological activity of herbs and spices, and particularly their medicinal and antimicrobial properties is due in the most part to EO [72]. The EO are used traditionally by humans, for many centuries, due to their numerous applications. They are used principally as flavors and fragrances in food and perfumery industries and due to their antimicrobial activity EO are also important for food and cosmetic preservation and for the control of human, animal and plant diseases [71]. These compounds can be used in the treatment of infections, due to the fact that are safe products for human and animal health [73].

The antibacterial and antioxidant properties of many EO and constituents have been studied so far [62]. Several EO are known for their strong antimicrobial activities against pathogenic and non-pathogenic bacteria, molds and fungi [74-76]. The biological activities of EO are related with their chemical composition and functional groups. Moreover, the power of essential oils is connected with their main constituents. The oils containing phenols such as thymol, carvacrol and eugenol, exhibit the most pronounced activity against diverse microorganisms [74].

Methanolic extracts of *Cuminum cyminum*, which contain methyl eugenol, an EO with an aromatic ring, inhibited swimming and swarming motility, QS, EPS production and biofilm formation by *P. aeruginosa*, *Proteus mirabilis* and *Serratia marcescens* [77]. EO from *Cinnamomum cassia* and their components, cinnamaldehyde and eugenol, affected the biofilm formation by *Escherichia coli*, interfering with their swimming motility, potential of adhesion and structure [78]. Moreover, cinnamaldehyde, inhibited QS of *E. coli* and *Vibrio harveyi*, affecting acyl homoserine lactones and autoinducer-2 that mediate QS [79]. In other work performed by Khan et al. [47], plant EO, such as clove, cinnamon, peppermint and lavender, also exhibited QS inhibition (QSI).

Table 1 Use of dietary phytochemicals for biofilm prevention and control, and their interference with motility, adhesion and Q-S.

	Phytochemical	Biofilm action	References
Essential oils (EO)	*Cuminum cyminum*: methyl eugenol	Inhibition of motility (swimming and swarming), EPS production and biofilm formation by *P. aeruginosa*, *P. mirabilis* and *S. marcescens*	[77]
	Cinnamomum cassia: cinnamaldehyde and eugenol	Interference with motility, adhesion and biofilm formation by *E. coli*; QS inhibition of *E. coli* and *V. harveyi*	[78, 79]
	Clove, cinnamon, peppermint and lavender	QS inhibition	[47]
	Thyme and oregano: carvacrol and thymol	Control dual-species biofilm formation by *S. aureus* and *S. enterica* Typhimurium. Suppress biofilm of *Salmonella* spp., *S. aureus* and *S. epidermidis*	[73, 80, 81]
Phenolics	Polyphenolics/polyphenols, polyanacardic acid, polysalicylic acid, catechin, epigallocatechin and tannic acid	Anti-adhesive properties and inhibition of biofilm formation of *S. mutans*; Inhibition of biofilm formation by *P. aeruginosa*	[82-86]
	(-)-epigallocatechin gallate, (+)-catechin and tannic acid	Interference with QS and inhibition of biofilm formation by *E. coli* and *P. putida*. Decrease of EPS production by *Staphylococcus* spp.	[87, 88]
	Extracts of *Rubus ulmifolius*: ellagic acid	Inhibition of biofilm formation of strains of *S. aureus*	[89]
	phloretin	Reduction in biofilm formation by enterohemorrhagic *E. coli* O157:H7	[90]
	Naringenin and quercetin	Inhibition of biofilm formation by *V. harveyi* and *E. coli* O157:H7	[91]
	Apigenin	Inactivation of biofilms of *S. sobrinus*	[92]
	Gallic and ferulic acids	Inhibition of motility and adhesion, biofilm prevention and control for *E. coli*, *P. aeruginosa*, *S. aureus*, *L. monocytogenes*; Biofilm inhibition of *S. mutans*	[21, 93, 94]
Isothiocyanates (ITCs)	Allylisothiocyanate, 2-phenylethilisotiocyanate	Interference with adhesion of *S. aureus*; Inhibition of motility and adhesion, biofilm prevention and control of *E. coli*, *P. aeruginosa*, *S. aureus*, *L. monocytogenes*	[95, 96]
	Extracts of *Brassica nigra*: allylisothiocyanate	Interference with adhesion of *Pseudomonas* sp.	[97, 98]
	Phenylisothiocyanate	Inhibition of motility and adhesion, biofilm prevention and control of *E. coli* and S. *aureus*	[99]
	Iberin	QS inhibition of *P. aeruginosa*	[49]
	Garlic: organosulfur compounds derived from garlic, such as allicin and ajoene	QS inhibition of *P. aeruginosa* and *E. coli*	[100-105]

Carvacrol is an EO component recognized as a safe food additive that has antimicrobial activity against bacteria, fungi and yeast. However, their potential for biofilm control has not been studied extensively. In a study performed by Knowles et al. [80], this natural compound demonstrated capacity for control dual-species biofilm formation by *S. taphylococcus aureus* and *Salmonella enterica* serovar Typhimurium, at various stages of maturation. EO of thyme and oregano and their constituent carvacrol also suppress biofilm formation of *Salmonella* spp strains. [81]. Furthermore, the activity of oregano oil and its major phenolic components, carvacrol and thymol were also tested against biofilms of *S. taphylococcus aureus* and *Staphylococcus epidermidis*. The results of this study showed attenuation of biofilm formation using sub-inhibitory concentrations of the oils [73].

3.1.2. Phenolics

Phenolic compounds or polyphenols are among the most important and abundant plant secondary metabolites. This diverse group of phytochemicals is classified into many subclasses, namely: simple phenolics, phenolic acids, coumarins, flavonoids, chalcones, benzophenones, xanthones, stilbenes, quinones, lignans and polyphenols [106, 107]. Phenolics can be found in diverse dietary products, such as vegetable, fruits, chocolate and beverages [63, 108].

Phenolics are considered potential therapeutic agents against a wide range of ailments including neurodegenerative diseases, cancer, diabetes, cardiovascular dysfunctions, inflammatory diseases and also against aging [63, 64, 109]. Therefore, foods containing phenolics are becoming an important part of diets due to their biological effects, mainly antioxidant potential and also antimicrobial properties. Also, recent findings indicate that some natural phenolic products commonly found in plants have anti-biofouling potential.

Anti-adhesive properties of some polyphenolic products against the ability of *Streptococcus mutans* to adsorb to saliva-coated hydroxyapatite and glass, as adhesion surfaces, were observed [82-84]. In another study, Sendamangalam et al. [85] investigated the anti-biofouling effects of polyphenols and the relationship between the inhibition of enzymes produced by *S. mutans* and their biofilm formation ability. These authors found that enzyme inhibition can lead to a decreased biofilm formation.

The anti-biofouling activities of 8 selected natural phenolic compounds (anacardic acid, polyanacardic acid, salicylic acid, polysalicylic acid, polyphenol, catechin, epigallocatechin and tannic acid) were tested against *P. aeruginosa*. All the phenolic compounds showed a significant reduction in biofilm formation by *P. aeruginosa* compared with the control [86]. Biofilm formation by enterohemorrhagic *E. coli* O157:H7 was markedly reduced with the antioxidant phloretin (found in apples), through repression of several genes, including those encoding toxins, AI-2 importer genes, curli genes and fimbria production [90]. Biofilm formation of various *S. aureus* strains, was inhibited by extracts of *Rubus ulmifolius* Schott., Rosaceae (Elmleaf blackberry), which are rich in the polyphenol ellagic acid and glycosylated derivatives [89]. Ellagic acid alone was also shown to possess antibiofilm properties [89].

Some polyphenolic compounds having a gallic acid (phenolic acid) moiety ((-)-epigallocatechin gallate, **(+)-**catechin and tannic acid) shown positive interference with bacterial QS of *E. coli* and *Pseudomonas putida*, blocking AHL [87]. Inhibition of biofilm formation by *E. coli*, *P. putida* and *B. cepacia* was also observed. Moreover, epigallocatechin gallate was also demonstrated to have several antibacterial properties, including the ability to decrease EPS production by *Staphylococcus* spp. [88].

In recent studies performed by Borges et al. [21], two phenolic acids (gallic acid and ferulic acid) demonstrated potential to inhibit bacterial motility, adhesion and to prevent and control biofilms of four pathogenic bacteria (*E. coli*, *P. aeruginosa*, *S. aureus* and *Listeria monocytogenes*). Moreover, Kang et al. [93] found that gallic acid can inhibit the growth of oral pathogens as well biofilm formation by *S. mutans* and proposed that this product may be used to prevent the formation of oral biofilms. Ergün et al. [94] demonstrated that simple aromatic esters of ferulic acid inhibited biofilm formation by *S. aureus* at concentrations lower than 8 μg/mL.

Naringenin and quercetin are flavonoids found in citrus species, which are antagonists of homoserine lactone and AI-2-mediated cell–cell signaling in *V. harveyi*. These compounds were able to inhibit biofilm formation by *V. harveyi* BB120 and *E. coli* O157:H7 in a dose-dependent manner [91]. Apigenin a flavonoid that is a biologically active compound of propolis (a resinous hive product secreted by *Apis mellifera* bees), inactivated biofilms of *Staphylococcus sobrinus* in dental plaque of rats [92].

3.1.3. Isothiocyanates - Glucosinolate hydrolysis products (GHP)

GLS are organosulfur compounds that can be found in large number of edible plants, such as the member of *Brassicaceae* family (i.e. cabbage, broccoli, mustard, horseradish and wasabi). Based on their chemical structure, they are grouped into aliphatic, aromatic and indole. These compounds are released during consumption of cruciferous vegetables due to hydrolysis by myrosinase enzyme (β-thioglucosidase enzyme) [65, 67, 110]. Intact GLS do not show antimicrobial activity, but the glucosinolate hydrolysis products - GHP [isothiocyanates (ITCs), nitriles, epithionitriles and thiocyanates] are active against clinical important microorganisms [65, 111]. Among GHP, ITCs are considered the most important biological active product. Their activity has been predominantly demonstrated against bacteria in planktonic states [55, 112-115]. Biofilm control was also observed but is less frequent [96, 97, 116, 117]. The presence of such compounds in natural foods is extremely interesting because, in most cases, vegetables are nontoxic to humans and readily available. Furthermore, functional food aliments with beneficial effects for health have attracted the attention of researchers and doctors, and can be used as a prophylactic treatment.

Lee and coworkers [95] demonstrated that allylisothiocyanate (an aliphatic ITC) interferes with the expression of genes related to adhesion of *S. aureus*. Guiamet and Gómez De Saravia [97], found that aqueous extracts of *Brassica nigra*, where the main component is allylisothiocyanate, had good activity to reduce planktonic cell growth and the number of adhered cells of *Pseudomonas* sp. Similar results were obtained by Gómez De Saravia and Gaylarde [98]. Moreover allylisothiocyanate and 2-phenylethilisotiocyanate demonstrated capability to prevent and control biofilm formation of *E. coli*, *P. aeruginosa*, *S. aureus* and *L. monocytogenes* [96]. Interference with motility and adhesion was also found with these compounds. Phenylisothiocyanate, other ITC, allowed both biofilm prevention and control for *E.*

coli and *S. aureus*. This compound also affected the adhesion process and motility of these bacteria [99]. A study realized by Jakobsen and coworkers [49] showed that iberin, an ITC produced by horseradish and many other members of the *Brassicaceae* family, had potent activity in QSI, blocking the expression of genes regulated by QS in *P. aeruginosa*.

Garlic possesses antibiotic properties that have been attributed to the presence of the compound allicin, an organosulfur compound such as ITCs [100]. Studies *in vitro*, performed with garlic extracts demonstrated that biofilms of *P. aeruginosa* previously treated with these extracts were more susceptible to treatment with the antibiotic tobramycin and to graze by polymorphonuclear (PMN) leukocytes. Moreover garlic extracts have shown the ability to clear pulmonary *P. aeruginosa* infections in a mouse model. These activities are dependent of the QSI [101-104]. Structurally similar garlic derived organosulfur compounds also inhibited biofilm formation by *P. aeruginosa* and *E. coli* through QS inhibition [105]. Natural products with capacity for inhibit QS can be used at the same time of antibiotics as adjuvants for increase the susceptibility of infecting bacteria [105]. Indeed, it has recently been demonstrated by Brackman et al. [118] that QS inhibitors increase the susceptibility of bacterial biofilms to multiple types of antibiotics.

4. Conclusions

The capacity of biofilm-embedded cells to resist to antibacterial compounds increased the interest in the search of new agents that are effective against bacteria in this mode of growth. In this context, many species of plants provide an enormous diversity of phytochemicals with a range of biological effect, namely antimicrobial properties against clinical relevant microorganisms. Moreover, it is known that phytochemicals act through different mechanisms from those of synthetic drugs, which make these compounds ideal candidates to reduce bacterial infections. Some phytochemicals have also the capacity to control bacterial biofilms, affecting nonessential processes for microbial growth. Several steps in the process of biofilm formation have been studied as target for novel drugs, including bacterial adhesion, motility and QS. An advantage of this approach is the fact that bacterial resistance is less probable, thus overcoming the problem of selective pressure verified with conventional antibiotics.

Overall, it is possible to conclude that a number of evidences suggest that dietary phytochemicals, such as essential oils, phenolics and isothiocyanates, have potential to become antimicrobial agents for the treatment of biofilm infection. Although the positive results to prevent and control biofilms, more studies would be essential to test the safety and the efficacy of these compounds. Diets rich in these compounds could be used as prophylactic treatment and correlated with a decreased risk of developing infections.

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