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Recent insights into anti-adhesion inhibition in medical implants to treat bacterial infections through naturally derived compounds

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Abstract
Bacterial infections are the leading global cause of illness and mortality. Since bacteria attaching to host cells is one of the primary causes of infection, advanced methodologies are to be introduced that will thwart the growth of bacteria from adhering to host tissues or remove them from tissues in the early stages of infection. The antibiotic therapeutic strategy has become less effective in the treatment of many bacterial diseases due to the perturbing antibiotic resistance developed by bacteria, where the addressed anti-adhesion compounds of an almost insignificant impact on their growth and pathogenesis. In this context, there arises a secondary quandary of biofilm formation on several medical implants that are in general made up of different materials, like alloys like stainless steel and titanium, on which the bacterial growth takes place. This aggravates the problem to the utmost level, posing a serious threat to the lives of the patients bearing the same contributing morbidity in the long run. In this article, we examine a number of anti-adhesion therapeutic strategies through the use of several natural compounds isolated from various organisms as effective formulations to meet the menace of anti-biofilm formation.

Keywords: Anti-adhesion, anti-biofilm, antibiotic resistance, medical implants

Introduction
The universal ability of microorganisms to adhere to surfaces and create extracellular polysaccharides leads to the development of biofilms. Due to the increasing resistance of biofilm-associated organisms to antimicrobial drugs and the potential for these organisms to infect patients with indwelling medical devices, biofilms pose a severe threat to public health (Donlan 2022) [59]. Each cell in a biofilm has a different physiology, with persistent, metabolically quiescent, and inactive cells serving as the prime examples (Bjarnsholt *et al.* 2018) [2]. Recent genetic and molecular techniques have uncovered genes involved in bacterial and fungal biofilms as well as regulatory networks necessary for the initiation of cell-surface contacts, biofilm maturation, and the return of biofilm microorganisms to a planktonic mode of development (O'Toole *et al.* 2000) [3]. A number of *in vitro* models have been employed to clarify the developmental phases and procedures necessary for the production of a *C. albicans* biofilm, and more recent research has started to identify the genetic regulation of the biofilm. It is evident that interactions between cells and their substrates, hyphal differentiation, and the creation of extracellular matrices are crucial to the establishment of biofilms (Blankenship *et al.* 2006) [4]. According to studies on the development of biofilms in Biofilm Airlift Suspension (BAS) reactors, it is hypothesized that the biofilm structure is determined by the relationship between biofilm surface loading and shear rate. Only a patchy biofilm will form under relatively strong shear pressures, but at low shear rates, the biofilm becomes very heterogeneous with many holes (Van Loosdrecht *et al.* 1995) [5]. It is believed that a variety of biofilm-specific traits, such as sluggish development and physiologic variability in the residents, are responsible for the resistant nature of biofilms, which is not fully understood. The sticky matrix, which can contain DNA and other polymers but is often predominately made of exopolysaccharides, is another crucial characteristic that strengthens biofilm resilience (Jefferson *et al.* 2004) [6].

Biofilm infections break down barriers such as epithelial surfaces engaged in chronic wounds, mucosal surfaces associated with chronic urinary tract infections, or intrinsic anomalies in endothelial linings contributing to infective endocarditis (Moser *et al.* 2007) [60]. Opportunistic microorganisms frequently cause infections in people with impaired immune systems as a result of underlying illnesses or medical procedures like surgery. The necessity to replace the contaminated equipment frequently results in considerably higher expenses for public health systems and a major hardship for the patient. The primary cause of the necessity to replace infected devices rather than treat them with antibiotics is that these infections frequently result in the formation of biofilms (Le *et al.* 2019) [8]. Biofilms are the major form of microbial life and are a biologically active matrix of cells and extracellular substances in association with a solid surface (Donran *et al.* 2001) [1]. All medical equipment is susceptible to the colonization of microbial infections. Medical devices are responsible for roughly 60-70% of hospital-acquired infections, particularly in critically ill patients (Rodrigues *et al.* 2011) [10]. Bacterial biofilm infection consequently may spread from implanted devices causing tissue damage, systemic spread of the infection (Schierholz 2001) [11] and dysfunction of the device, resulting in significant disease and death. The main microorganisms responsible for biofilm development on indwelling medical devices are Gram-positive [*Enterococcus faecalis,* (Kristich *et al.* 2004) [12] *Staphylococcus aureus,* (Geoghegan *et al.* 2010) [13] *Staphylococcus epidermidis,* (Fey *et al.* 2010) [14] and Gram-negative bacteria like *Escherichia coli,* (Sharma *et al.* 2016) [15] *Klebsiella pneumoniae,* (Vuotto *et al*. 2014) [16] *Proteus mirabilis,* (Holling *et al.* 2014) [17] as well as yeasts (*Saccharomyces cerevisiae)* (Veerachamy 2014) [18]. Increased resistance to harmful environmental factors, such as resistance to antibiotics and antimicrobial agents, is brought on by the formation of Biofilm. It is critical to find novel antibacterial drugs that can control biofilm formation and growth since biofilms play a key role in infectious illness and the spread of multi-drug resistance. The crystal violet test is the most extensively used method to determine the anti-biofilm capability of natural compounds, though it has some drawbacks, such as frequent washing, which can result in cell death and biofilm disruption. The Tissue Culture Plate (TCP) technique (Allemailem *et al.* 2022) [19] which is a relatively reliable alternative to the Congo Red Agar (CRA) (Ramachandran *et al.* 2017) [20] and Tube methods (Ashajyothi 2016) [21] is another method used to test the antibiofilm effects of natural products. It is widely known that herbal treatments have been used for centuries by many human societies, and some of those organic materials are crucial for the treatment and prevention of infectious illnesses. For instance, traditional Chinese medical herbs were frequently employed in the treatment and prevention of bacterial infections, and several plants, such *as Scutellaria* (Liu *et al.* 2023) [22] and *Tussilago* (Boucher *et al.* 2020) [23], have antibacterial properties. There are hundreds of different types of plants on the globe, and because traditional medicinal plants have a long history of being used to treat infectious diseases, particularly in India, these plants may be rich sources and provide the best chances for producing novel anti-biofilm medicines (Lu *et al.* 2019 & Danquah *et al.* 2022) [24, 25]. This review will typically focus on the mechanism of the biofilm formations on different medical implants and the thorough exploration of naturally derived compounds that can challenge the predicament of bacterial adherence.

Biofilm formation: Reasons and Mechanisms

A bacterial biofilm is a mass of bacterial cell clusters that have attached themselves to a surface. Biofilms are the most prevalent type of bacteria in infected tissue and natural habitats. The glycocalyx matrix is supportive of bacteria's resistance to antibiotics and other antimicrobial agents (Bjarnsholt 2013) [26]. Within biofilm, genetic adaptation is necessary to lower vulnerability and adopt a relatively protected and distinctive phenotype (Stewart 2002) [27]. In order to cohere and adhere the biofilm to the solid surface and to aid in the growth of the biofilm, glycocalyx uses electrostatic, Van der Waal, and hydrogen bond forces (Burtseva 2021) [28]. Different environmental factors have an impact on the biofilm capsules' constituents, such as glycoproteins and polysaccharides (Eddenden *et al.* 2020) [29], Alginate (Scoffield *et al.* 2017) [30] and galactosamine galactose (Lee *et al.* 2016) [31]. The glycocalyx matrix supports bacterial resistance to antimicrobial agents and other antimicrobial agents, including antibiotics. The variations in nutrition and oxygen availability within biofilms have an impact on the bacterial growth rate and metabolic activity. Different concentrations of metabolic substrates and products were used to demonstrate the amount of bacterial growth and activity inside the biofilm as is observed in *Clostridia* (Singh *et al.* 2017) [32].

Biofilm Formation of Medical Implants

Infections linked to biofilm in medical devices are a severe threat to the public's health and have a negative impact on the device's performance and Stainless steel and other alloys like aluminum and titanium are utilized in the construction of medical implants used in orthopedic and oral surgery. Osseointegration -a sustained transmission and distribution of stress from the implant to and within the bone tissue is required for contact to be formed between normal, remodeled bone and an implant without the interposition of non-bone tissue (Jayesh *et al.* 2015) [33], and its antimicrobial effects, fundamentally depend on the form of the surface as well as the chemical composition of the device. Different bacterial surface-attached proteins - some of which are unclear - help to promote early adherence and biofilm growth (Veerachamy *et al.* 2014) [18].

Lens: Mechanism of Biofilm Formation and Effect

The pathophysiology of postoperative endophthalmitis appears to be influenced by bacterial binding to intraocular lens implants (IOLs) and bacterial colonization of IOLs. The most typical bacterium isolated in instances of postoperative endophthalmitis is *Staphylococcus epidermidis*. (Hosseini *et al.* 2012) [35]. Although this bacterium is typically thought to have limited pathogenic potential, mounting evidence suggests that it is involved in a number of eye illnesses. *S. epidermidis* regularly colonizes the surfaces of synthetic devices such as artificial hearts, total joint replacements, and vascular prostheses, and its adherence to IOL materials has lately received attention in the literature (Okajima *et al.* 2006) [36]. When wearing contacts for an extended period of time, biofilm buildup on the lenses may contribute to MK. Etafilcon A, galyfilcon A, lotrafilcon A, balafilcon A, and others were examined by Imamura *et al*. for contact lens

brands like Polymacon and Alphafilcon A, and their findings showed that few bacteria were clinically isolated on all varieties of lenses and created biofilms. In addition, it was shown that the lens had an impact on the biofilm's architecture (Kackar *et al.* 2017) [37].

Orthopedic Implants: Mechanism of Biofilm Formation and Effect

Bacterial biofilm infection consequently causes tissue to be destroyed when gets infected through implants, the disease to spread throughout the body, and the device starts to malfunction Gram-positive and Gram-negative bacteria, as well as yeasts, are the principal microorganisms in charge of biofilm development on indwelling medical devices. *S. epidermidis* was predominantly prevalent in the surrounding tissue and co-localized with macrophages in titanium implants that were either pre-seeded with the bacterium or carried a pre-grown *S. epidermidis* biofilm (Riool *et al.* 2014) [38]. Large numbers of *S. epidermidis* were cultivated from the tissue, indicating that many of the bacteria were still alive. Therefore, a contaminated implant may serve as a source of infection for the tissue around it since bacteria may live inside cells. The prevention and treatment of bacterial-related infections are hindered by the fact that these infections are resistant to immune defense systems (Harding *et al.* 2014) [39]. The main explanations for the reduced effectiveness of antibiotics against biomaterial-related illnesses are thought to be the sessile bacteria's diluted susceptibility and the drugs' poor penetration into the biofilm matrix (Esteban *et al.* 2012) [40]. Almost all medical implants and devices, including prosthetic heart valves (Jamal *et al.* 2018) [41] orthopedic implants (Li *et al.* 2018) [42], dental implants (Pye *et al.* 2009) [43] intravascular catheters (Mermel *et al.* 2000) [44] cardiac pacemakers (Marrie *et al.* 1982) [45], contact lenses (Cheung *et al.* 2016) [46] etc. have been linked to microbial infections. Osteomyelitis is a disorder caused by infections connected to biomaterials used in orthopedic applications (Jia *et al.* 2022) [47].

Catheter: Mechanism of Biofilm Formation and Effects

The colonization of biofilm around non-surgical indwelling medical devices, mostly in urine catheters, that can begin either at the site of insertion in the skin or after the catheter has been implanted (Donlan 2002) [9].

The bacteria starts to produce and gather proteins, polysaccharides, and DNA to create a biofilm once it has established a firm bond with the surface. (Thallinger *et al.* 2013) [50]. Clinical issues brought on by biofilm infections include illness, persistent inflammation, poor wound healing, rapidly developing antibiotic resistance, and the development of infectious emboli (Bryers *et al.* 2008) [51]. It has been reported that many bacteria can cause prosthesis-related infections, such as *S. aureus*, including methicillin-resistant strains (MRSA), coagulase-negative *Staphylococci* (CNS) to name a few (Okajima *et al.* 2006 & Veerachamy *et al.* 2014) [36, 18].

Natural Compounds: Breakthrough of Biofilm Formation

Natural products have traditionally been a rich source of varied chemical matter with a variety of biological functions and have been crucial in the development of many drugs, particularly those for infectious diseases. Numerous substances found in plants, microorganisms, and marine life have been found to have anti-biofilm activity. Total synthesis and medicinal chemistry programs have aided in structure confirmation, the identification of crucial structural motifs, a better understanding of mechanistic pathways, and the development of more potent, readily available, or pharmacologically advantageous derivatives of anti-biofilm natural products (Melander *et al.* 2020) [52].

The rate of progress in modern science and technology is quickening. The identification and creation of novel, plant-derived drugs with enhanced therapeutic efficacy and decreased negative effects, crude extracts of leaves, roots, and stems, as well as specific chemicals extracted from these essential oils and oil components, are all plant-derived substances that are now the subject of significant investigation for potential uses (Ahmad *et al.* 2014) [53]. Many bacterial species and antimicrobial peptides (AMPs), generated by many cells in the human body as well as those of other animals, consider the synthesis of extracellular enzymes or surfactants, which result in the breakdown and solubilization of sticky components in the biofilm matrix (Fig. 1) as the primary mechanism of biofilm disassembly. (Roy *et al.* 2018 & Lopes *et al.* 2022) [55, 54]. Table 1 provides a thorough evidence of the effectiveness of natural compounds that can well combat the genesis of the biofilm formation.

Table 1: Role of natural compound in anti-biofilm formation

Type of Compound	Effect on Biofilm	Reference:
Amikacin [isolated from *Microsporum canis*]	Exhibit broad-spectrum antibacterial action by altering protein folding against both *P. aeruginosa* and methicillin-resistant *S. aureus*	(Lopes *et al.* 2022) [54]
Garlic extract	Garlic extract increased *S. mutans* adhesion to orthodontic wire while having a demonstrated antibacterial impact on all microorganisms.	(Lee *et al.* 2011) [56]
Cathelicidins [isolated from the intestinal tissues of *Myxine glutinosa*]	Prevents *Staphylococcus epidermidis* from adhering to artificial surfaces and from forming biofilms	(Hell *et al.* 2010) [57]
Patriniae	Decreased exopolysaccharide synthesis and prevented biofilm development	(Lu *et al.* 2019) [24]

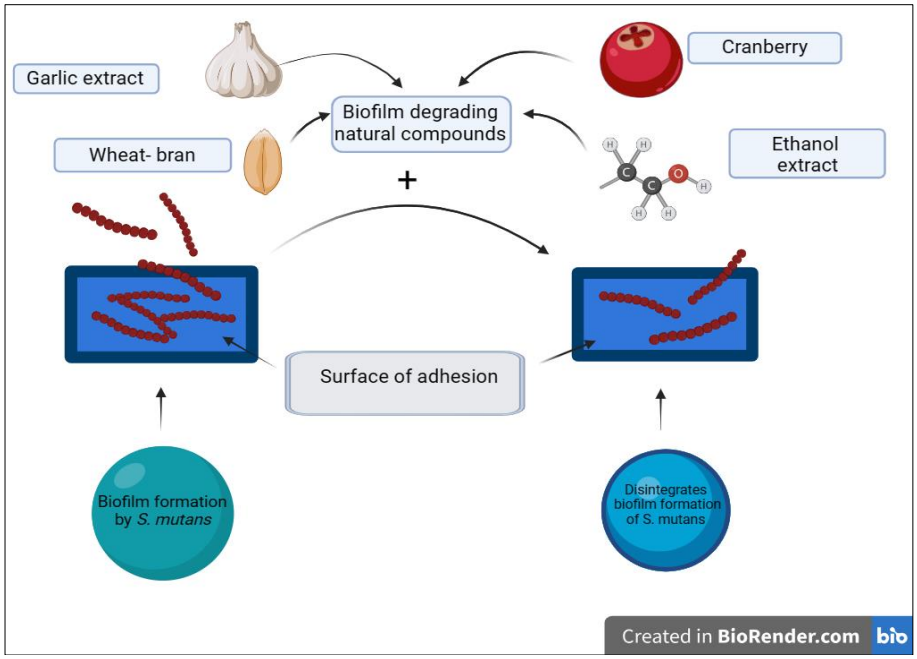

Fig 1: Schematic representation of the use of natural compounds in combating biofilm formation (Image created through Biorender)

Conclusion and Future Perspective

The use of naturally derived compounds for anti-adhesion inhibition in medical implants to treat bacterial infections shows great promise as a potential solution as their dwelling on medical implants poses threat to lives. The most economical as well as feasible resort can be through the use of naturally derived compounds, such as plant extracts or antimicrobial peptides, that have the potentiality to disrupt bacterial adhesion to implant surfaces and thus can reduce the incidence of implant-associated infections. These natural compounds often have good biocompatibility that can minimise the risk of adverse reactions in patients. Smarter ways can be evolved through incorporating naturally derived compounds into the indwelling device of need to inhibit bacterial adhesion that represents an exciting avenue for improving patient outcomes and reducing the burden of implant-related infections. However, rigorous testing and clinical trials are necessary to validate the safety and efficacy of such treatments.

Conflict of Interest

The authors have no potential conflict of interest.

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