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A review on antimicrobial strategies in mitigating biofilm-associated infections on medical implants

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ABSTRACT

Biomedical implants are crucial in providing support and functionality to patients with missing or defective body parts. However, implants carry an inherent risk of bacterial infections that are biofilm-associated and lead to significant complications. These infections often result in implant failure, requiring replacement by surgical restoration. Given these complications, it is crucial to study the biofilm formation mechanism on various biomedical implants that will help prevent implant failures. Therefore, this comprehensive review explores various types of implants (e.g., dental implant, orthopedic implant, tracheal stent, breast implant, central venous catheter, cochlear implant, urinary catheter, intraocular lens, and heart valve) and medical devices (hemodialyzer and pacemaker) in use. In addition, the mechanism of biofilm formation on those implants, and their pathogenesis were discussed. Furthermore, this article critically reviews various approaches in combating implant-associated infections, with a special emphasis on novel non-antibiotic alternatives to mitigate biofilm infections.

1. Introduction

Bacterial biofilms are communities of various microorganisms that adhere to any surfaces and are enveloped within Extracellular Polymeric Substances (EPS) matrix (Vestby et al., 2020). EPS consists of proteins, lipids, polysaccharides, and extracellular DNA, which contribute to the biofilm's antimicrobial resistance (Mishra et al., 2020). Biofilm-related infections are responsible for approximately 80 % of all microbial infections, including endocarditis, osteomyelitis, cystic fibrosis, rhinosinusitis, periodontitis, and prostheses and implantable devices (Khatoon et al., 2018). Implants are medical devices used to provide structural support to various organs in the human body including bones, joints, breasts, hips, mitral valve, teeth, cardiac stents, and biliary stents which can be made of metals, rubber, mesh-like materials, synthetics, or plastics (Kandi and Vadakedath, 2020). Biofilms on implants are caused by both Gram-positive and Gram-negative pathogens such as *Enterococcus faecalis* (*E. faecalis*), *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis* (*S. epidermidis*), *Streptococcus viridans* (*S. viridans*), and *Pseudomonas aeruginosa* (*P. aeruginosa*) (Govindarajan et al., 2020; Khatoon et al., 2018). Biofilm infections on implant surfaces can lead to implant failure, chronic infections, and high mortality rates. In particular, biofilms are a major cause of implant failure in implants such as cochlear implants, orthopaedic implants, cardiac implants, urological implants, hernia surgical mesh implants, spinal implants, breast implants, and urinary catheters. As a result, the majority of implantable medical devices carry the risk of biofilm-associated infections that significantly impact on lifestyle and also fatal. In the United States alone, over 500,000 cases per year was recorded on biofilm infections on implants (Khatoon et al., 2018), such infections lead to implant failure and often require surgical restoration. In particular, biofilms formation on prosthetics often requires revision surgery, and the predicted healthcare expenses for revision surgery in the US alone are over $500 million and this number is expected to increase to $1.62 billion by 2030 (Kurtz et al., 2007).

Pathogenic bacteria residing in biofilms possess a wide range of virulence proteins on their surface, enabling them to adhere to and colonize both implants and host tissues (Govindarajan and

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Kandaswamy, 2022; Kandaswamy et al., 2013; Shanmugasundarasamy et al., 2022). To mitigate biofilm attachment and associated implant failure, various strategies were practiced till date. For instance, the use of chlorhexidine during the perioperative period has demonstrated efficacy in reducing biofilm-related complications and implant failure (Daubert and Weinstein, 2019). In addition, antimicrobial compounds derived from plants and nanoparticles (conjugated with plant-derived phytochemicals) were proven to be effective in preventing bacterial colonization and formation of biofilm on dental implants (Govindarajan et al., 2023; Sivaramakrishnan et al., 2019). In the case of cochlear implants, the application of soft polymers such as Polydimethylsiloxane (PDMS) coated with antimicrobials (at a thickness of 10–40 nm) has been found to significantly inhibit bacterial cell accumulation (Goldfinger et al., 2014). Additionally, phytochemicals derived from *Melaleuca alternifolia* (*M. alternifolia)* have demonstrated efficacy in controlling biofilm growth (Brady et al., 2010). Synthetic bioactive glass (BAG) has also emerged as a valuable approach for reducing biofilm formation (Chen et al., 2023). In orthopaedic implants, antimicrobial approaches involve the use of antibiotics, nanoparticles, metal ions, metal oxides, hydrophilic polymers, quaternary ammonium compounds (QACs), biomolecules such as antimicrobial peptides (AMPs) and chitosan (Chen et al., 2023). In addition to antibiotics, non-antibiotic substances such as quorum-sensing inhibitors and antimicrobial peptides were considered to be potential anti-biofilm agents. Together, these strategies offer the potential for addressing biofilm-related complications and enhancing the overall success of implants in the long term (Dzhemiliev et al., 2023; Khoo and Grinstaff, 2011).

Considering the significant risks associated with biofilm formation and the economic implications of implant failure, it is vital to comprehend the preventive strategies employed in clinical settings. This comprehensive review explores the mechanism of biofilm formation on diverse surfaces, including dental, orthopedic, cochlear, tracheal implants, and various prostheses. Moreover, the article critically assesses the advantages and disadvantages of different therapeutic approaches aimed at preventing implant failures. Additionally, it highlights the potential of non-antibiotic strategies in effectively addressing biofilm-associated infections in biomedical implants. Usage of non-antibiotic compounds as implant coatings are particularly important, as excessive usage of antibiotics have resulted in emergence of drug resistant strain and gastrointestinal disturbances due to imbalance in gut microbial flora (Govindarajan et al., 2024; Mohsen et al., 2020). In summary, this article critically evaluates the potential use of non-antibiotic compounds such as Quorum Sensing (QS) blockers and virulence inhibitors as effective implant coating materials.

2. Biofilms on dental implants and the role of quorum sensing inhibitors as antimicrobial compounds

2.1. Bacterial colonization and biofilm formation on dental implants

Implants used in oral restoration are susceptible to biofilm formation, impacting oral health. It provides an ideal surface and environment for bacterial colonization, much like a natural tooth. Surface modifications on implants enhance characteristics such as wettability, cell-implant interaction, cell proliferation, and osseointegration resulting in accelerated healing and reduced treatment time. However, they also promote bacterial colonization and formation of biofilm on dental implants (Dantas et al., 2016; Ponsonnet et al., 2003; Teughels et al., 2006). Oral biofilms are predominantly formed by Gram-negative anaerobic pathogenic strains like *Porphyromonas gingivalis* (*P. gingivalis*), *Spirochetes, Actinobacillus actinomycetemcomitans* that often lead to conditions like Peri-implant mucositis, Peri-implantitis, Denture-related stomatitis, Dental caries, Periodontitis, and Gingivitis (Pye et al., 2009; Spratt and Pratten, 2003).

Biofilm-forming bacterial species in dental implants can be classified into early and late colonizers. Early-stage infections were primarily dominated by *Streptococcus* spp. such as *Streptococcus oralis* (*S. oralis*), *Streptococcus mitis* (*S. mitis*), and *Streptococcus sanguinis* (*S. sanguinis*) along with phylotypes belonging to *Actinomyces, Veillonella, Gamella, Neisseria,* and *Prevotella* genera (Kolenbrander et al., 2006). In contrast, the later stages of infections were dominated by Gram-negative species such as *Fusobacterium nucleatum* (*F. nucleatum*), *P. gingivalis, P. aeruginosa, E. coli, and Treponema denticola* (*T. denticola*). Fully matured oral biofilms lead to conditions such as peri-mucositis, periodontitis, and peri-implantitis characterized by inflammation, bleeding, swelling, erythema in the soft tissues surrounding the implants, and marginal bone loss that supports implants, ultimately leading to implant failure (Greenstein and Cavallaro, 2014; Heitz-Mayfield and Salvi, 2018; Jepsen et al., 2018). Furthermore, implant failure can also be caused due to the lack of osseointegration during the initial stages. Osseointegration, a critical process in dental implant success, involves the integration of implants with the host bone through osteogenesis. However, this process can be influenced by competitive pathogen interaction followed by biofilm formation on the implant surface and the host tissue (Kligman et al., 2021).

The maturation process of plaque is presumed to be influenced by interactions between diverse bacterial cell types. These interactions manifest through various mechanisms such as cell-cell contact, metabolic cooperation, genetic exchange, and Quorum Sensing (Dhir, 2013; Kolenbrander et al., 2006). Initially, there is a weak and reversible binding between implant surface - pathogen and as the process progresses, an irreversible attachment happens between the bacteria and the surface. Saliva contains dietary carbohydrates, mucins, proteins, and glycoproteins which serve as the primary nutrient source for bacteria (Dhir, 2013). The tooth enamel is covered by a thin film known as the acquired pellicle, derived from salivary proteins. Proteins and glycoproteins act as binding agents that promote coaggregation and bacterial adhesion. The bacterial coaggregation is facilitated by molecules such as adhesins, particularly lectins, found on the pathogen surfaces. Gradual aggregation of bacterial colonies results in the formation of multi-layered cell clusters within the polymer matrix (Busscher and Van Der Mei, 1997). Planktonic bacteria and late colonizers rely on their receptors like fimbriae (type I and II) and also the receptors found in the saliva such as proline-rich peptides, proline-rich glycoproteins, alpha-amylase for successful attachment onto the tooth surface (Gibbons et al., 1991; Murray et al., 1992; Scannapieco et al., 1995).

Bacterial cells within biofilms produce specific signaling molecules such as Acylated Homoserine Lactones (AHLs), Competence Stimulating Peptides (CSPs), and Autoinducer-2 (AI-2) that function as messenger molecules and facilitate interspecies communication via QS system (Dhir, 2013; Kolenbrander et al., 2002). In addition, bacteria involved in biofilm formation secrete EPS, which immobilizes cells and promotes the formation of cooperative micro-consortia and cell-cell communication (Flemming and Wingender, 2010). EPS provides physical barrier to antimicrobial agents entry and maintaining the structural integrity of biofilms (Walters et al., 2003).

The substantial challenges posed by antimicrobial resistance and biofilm formation necessitate effective therapeutic strategies. These approaches involve destabilizing and inhibiting EPS synthesis, quorum quenching, and binding to bacterial adhesins, and cell wall proteins to prevent attachment and membrane disruption (Lu et al., 2019; Mishra et al., 2020). Bacterial quorum sensing relies on auto-inducers to stimulate population growth, facilitating synchronized actions and coordinated gene expression for the development of mature biofilms. Quorum quenching disrupts this communication, inhibits formation of biofilms, and reduces expression levels of virulence factors (Grandclément et al., 2016). Various methods can be employed to disrupt QS signals, including inhibiting the synthesis of signaling molecules, enzymatic degradation to prevent their accumulation above a threshold, blocking the binding of signal receptors using analogs, and obstructing the activation of target genes triggered by QS signals (Weiland-Bräuer, 2021). Several plant-derived compounds, such as Andrographolides (Lim et al.,

2021), Rosmarinic acid (Walker et al., 2004), Ajoene (Fiori-Duarte et al., 2023; Jakobsen et al., 2012), Quercetin (Ouyang et al., 2016; Quecan et al., 2019), Curcumin (Fernandes et al., 2023), 6-gingerol (Han-Shin Kim et al., 2015), allicin (Xu et al., 2019; Zhang et al., 2022), piperine and trichostachine (Vázquez-Martínez et al., 2020), have shown potent quorum quenching activity. Additionally, well-studied AHL-degrading enzymes include AHL-lactonases (Dong et al., 2002, 2000), AHL-acylases (Lin et al., 2003), and AHL-oxidoreductases were proven to reduce biofilm formation by blocking QS signaling pathway (Dong and Zhang, 2005; Zhu et al., 2023). Therefore, dental implants coated with the aforementioned QS blockers could potentially minimize the risk of biofilm-associated infections (Tables 1 and 2 and Fig. 1).

2.2. Candida fungal infections on dental implants

Candida albicans (*C. albicans*) is a dimorphic fungal pathogen predominantly found in oral cavities that causes candidiasis and major contributor to periodontitis which leads to soft tissue inflammation, and increased pocket depth thereby contributing towards implant failure (Canabarro et al., 2013; Krishnan et al., 2020). Other pathogenic Non-*C. albicans* Candida (NCAC) species that are associated with candidiasis include *Candida glabrata, Candida tropicalis*, and *Candida parapsilosis* (Li et al., 2007; Silva et al., 2012). Under physiologic conditions they remain as commensal (yeast) and under opportunistic conditions they become pathogenic (hyphae). This transformation in cellular morphology is governed by farnesol, an extracellular quorum-sensing molecule synthesized by *C. albicans* itself. When farnesol exceeds a specific threshold, it effectively blocks the shift from yeast to mycelium, leading to the prevalence of budding yeast (Hornby et al., 2001; Ramage et al., 2002). It was noted that there was an upregulation in the expression of virulent genes such as *SAP, PLB* and *LIP* genes responsible for adhesion and secretion of tissue-damaging hydrolytic enzymes and the expression of these virulence factors were dependent on other bacterial species colonizing the implant surface (Cavalcanti et al., 2016; Chaffin, 2008; Schaller et al., 2005). The primary hydrolytic enzymes involved in the pathogenicity of Candida species are secreted aspartyl proteinases, phospholipases, lipases, and hemolysins (Dostál et al., 2005; Portela et al., 2010; Schaller et al.,

Table 1
Potential antimicrobial coatings with bactericidal and biofilm inhibition activity for dental implants.

Substrate	Coating material/ Coating strategy	Susceptible species	Effectiveness of the coating	References
Titanium	Catechol (Cat) functionalized with citrate (Cit) and Silver (Ag) Nano-Particles (NPs) / citrate reduction and stabilization method	*P. aeruginosa, Bacillus subtilis* (*B. subtilis*)	0.645 nM of Cat-Cit-AgNPs coating inhibits *P. aeruginosa* and *B. subtilis* biofilms by 75 % and 65 %, respectively.	(Choudhury et al., 2019)
	Chitosan + AgNPs	*Streptococcus mutans* (*S. mutans*), *P. gingivalis*	Reduced bacterial adhesion, a 60 % decrease in the biofilm biomass were observed.	(Divakar et al., 2018)
	Copper coated Calcium Phosphate (CaP) coating/ electrodeposition technique	Gram positive- *Streptococcus gordonii* (*S. gordonii*), *Actinomyces naeslundii, Parvimonas micra.* Gram negative- *F. nucleatum, Aggregatibacter actinomycetemcomitans, Prevotella intermedia* (*P. intermedia*), *P. gingivalis*	A substantial decrease of at least 2 log units was observed in both Gram-positive and Gram-negative strains, as well as the overall flora.	(Pierre et al., 2023)
	Zinc oxide NPs (ZnO) and Hydroxyapatite NPs (HA)/ electrohydrodynamic deposition	*Streptococcus* spp., anaerobic and aerobic bacteria selectively isolated from human saliva.	The populations of *Streptococcus* spp. (2 log fold reduction), anaerobes (1.5 log fold reduction), and aerobes (1 log fold reduction) were significantly reduced on ZnO, HA, and ZnO + HA coated Ti discs.	(Abdulkareem et al., 2015)
	Graphene oxide-Ag NPs/ electroplating and UV reduction	*S. mutans, P. gingivalis*	100 μg/ml of graphene oxide showed potent antibacterial activity with 95.45 % effectiveness, along with reduced adhesion and altered membrane morphology.	(Jin et al., 2017)
	Totarol/ spin coating	*S. gordonii,* mixed oral bacteria (isolated from the saliva of two healthy volunteers)	Totarol coatings significantly reduce the density of *S. gordonii* films and oral bacterial biofilms, indicating contact killing and biofilm growth inhibition effects.	(Xu et al., 2020)
	Rhamnolipid (R89BS)/ Physical adsorption	*S.aureus, S. epidermidis*	The R89BS-coating resulted in a remarkable reduction of over 98 % in biofilm biomass for *S. aureus* and 54 % for *S. epidermidis*.	(Tambone et al., 2021)
		C. albicans, S. aureus	Coating significantly reduced fungal and bacterial cell numbers, with 92 % inhibition for *C. albicans* and 81 % for *S. aureus*. After 48 h, the coated samples exhibited thinner biofilms compared to uncoated samples.	(Tambone et al., 2021)
	GL13K (GL13KGKIIKLKASLKLL-CONH2) peptide/ Silanization	*P. gingivalis*	A notable decrease in colony forming units (CFUs) was observed. CFU and WST-8 staining results confirmed GL13K's bactericidal effect.	(Zhou et al., 2015)
	Fluorine- TiO_2 calcium phosphate (TiCP) coating/ micro-arc oxidation	*E. coli, S. aureus*	TiCP-F6 and TiCP-F9 (higher fluorine content) demonstrated 97 % antibacterial rates for 14 days and over 94 % on day 28, indicating long-term effectiveness.	(Zhou et al., 2018)
	Quaternized Silicon carbide (QSiC) coating/ RF-Magnetron Sputtering and Nitrogen Atom Quaternization	*P. gingivalis*	QSiC-coated titanium exhibited significantly lower biofilm coverage (9.74 %) compared to the uncoated group (85.2 %), resulting in an eight-fold reduction.	(Camargo et al., 2020)
	Triethoxysilylpropyl succinic anhydride silane (TESPSA)/ NaOH activation and silanization	*S. sanguinis, Lactobacillus salivarius* (*L. salivarius*), Oral plaque	The dead/live ratios were 0.4 and 0.5 for *S. sanguinis* and *L. salivarius* mono-species biofilms, and 0.6 in the oral plaque model.	(Buxadera-Palomero et al., 2020)
	Hexapeptide coating/ surface adsorption	*Veillonella parvula* (*V. parvula*), *Streptococcus sobrinus* (*S. sobrinus*), *P. gingivalis*	Coated discs reduced attachment of *V. parvula* and *S. sobrinus* by 25 % and *P. gingivalis* by 50 % compared to uncoated discs, preventing dental biofilm formation.	(Fang et al., 2020)

Table 2
Phytochemicals with potential anti-biofilm activity.

Compound	Source	susceptible species	Effectiveness of the phytochemical	References
Chelerythrine	*Bocconia cordata*	*C. albicans* and *S. aureus*	Single species: MIC= 4 μg/mL *$MBIC_{90}$= 2 μg/mL The MIC and MBIC concentrations were similar for both, *C. albicans* and *S. aureus*. Dual species: (*C. albicans* ± *S. aureus*): MIC= 6 μg/mL. $MBIC_{90}$= 3 μg/mL.	(Qian et al., 2020)
Warburganal, polygodial, alpha-linolenic acid (ALA)	*Warburgia ugandensis* Sprague subspecies *ugandensis*	*C. albicans*, *Candida glabrata*, *S. epidermidis*, *S. aureus*	*C. albicans*: BIC_{50} (warburganal)= 4.5 ± 1 μg/mL. BIC_{50} (ALA)= 10.8 ± 5 μg/mL. *S. aureus*: BIC_{50} (warburganal)= 37.9 ± 8 μg/mL. BIC_{50} (ALA)= 25 μg/mL with ALA.	(Kipanga et al., 2020)
Carvacrol	*Origanum vulgare*	*P. aeruginosa*	Carvacrol at 1.9 mM decreased C6-AHL production by 80% and reduced virulence by suppressing autoinducer levels and lasR gene expression, respectively.	(Tapia-Rodriguez et al., 2019)
Pulverulentone A	*Callistemon citrinus* Skeels	Methicillin-resistant *S. aureus* (MRSA), Methicillin-sensitive *S. aureus* (MSSA)	MIC= 125 μg/mL. The biofilm inhibitions were up to 71% in MRSA and 62.3% in MSSA biofilms. Staphyloxanthin biosynthesis in MRSA and MSSA was suppressed, resulting in inhibitions of 55.6% and 54.5%, respectively.	(Shehabeldine, Ashour, Okba, & Saber, 2020)
Essential oil (Thymol-1.991 g/ml, carvacrol -0.353 g/ml and their precursors)	*Lippia berlandieri* Schauer	*P. aeruginosa, Salmonella* Typhimurium (*S.* Typhimurium)	*S.* Typhimurium was more susceptible than *P. aeruginosa* and a complete biofilm inhibition of *S.* Typhimurium was observed at a concentration of 250 μg/mL.	(Reyes-Jurado et al., 2020)
Hydroginkgolic acid and Ginkgolic acid	*Pistacia lentiscus L.* fruit	*P. aeruginosa*	At 100 μg/mL concentration, a significant 82% decrease in pyocyanin production and also down-regulation of the phzA gene responsible for pyocyanin production was observed. IC_{50} value: 4.9 μg/mL.	(Tahrioui et al., 2020)
Epigallocatechin-3-Gallate-Stearate (EGCG-S)	*Camellia sinensis*	*S. mutans*	Complete biofilm inhibition was observed at 250 μg/mL concentration.	(Melok, Lee, Mohamed Yussof, & Chu, 2018)
Eugenol and Linalool	*Ocimum tenuiflorum*	*P. aeruginosa*	Eugenol: Pyocyanin production was reduced by 85.26±6.32% and maximum inhibition of 72.75±8.72% at 150 μg/mL. Rhamnolipid production was reduced by 82.67±7.82%. Linalool: Pyocyanin production was reduced by 70.14±7.25 % at 180 μg/mL and maximum inhibition of 66.68±8.25% at 175 μg/mL. Rhamnolipid production was reduced by 74.14±5.3.	(D Lahiri et al., 2021)
Hordenine	*Hordeum vulgare*	*P. aeruginosa*	MIC: 2.5 mg/mL. At concentration of 1mg/mL, C4-HSL production was reduced by 79% revealing anti-QS activity. Also, with an addition of 0.4 μg/mL of netilmicin antibiotic an 88% biofilm inhibition was observed.	(J.-W. Zhou et al., 2018)
Catechin	*Azadirachta indica*	*Alaligenes faecalis* (*A. faecalis*), *Pseudomonas gingivalis* (*P. gingivalis*)	Maximum efficacy was observed at 180 μg/mL. Carbohydrate and protein production was suppressed over 90%, QS activity was inhibited in both *P. gingivalis* & *A. faecalis*. Reduced DNA and RNA content in both the species was observed.	(Dibyajit Lahiri et al., 2021)
5-Hydroxymethylfurfural (5HMF)	*Musa acuminata* peel	*P. aeruginosa*	#BIC= 400 μg/ml (89%). Total proteins, EPS, and CSH production was inhibited by 79%, 82%, and 77%. Inhibited QS-related virulence factors, LasA protease (75%), LasB elastase (68%), pyocyanin (80%), Alginate (78%), and Rhamnolipid (69%).	(Vijayakumar & Ramanathan, 2020)
Ellagic acid	*Camellia nitidissima Chi*	*P. aeruginosa*	MIC= 150 μg/ml IC_{50}= 0.067 ±0.002 At a concentration of 10 μg/ml, pyocyanin production was reduced by 52.3%.	(R. Yang et al., 2018)
Malabaricone C	*Myristica cinnamomea*	*Chromobacterium. violaceum, P. aeruginosa*	Reduced violacein and pyocyanin production at concentrations ≥1mg/mL thereby inhibiting biofilm formation.	(Chong et al., 2011)

*$MBIC_{90}$ is Minimum Biofilm Inhibitory Concentration, #BIC is Biofilm Inhibitory Concentration

2005). In particular, phospholipases play a crucial role in host cell membrane damage and holds the capacity to expose additional receptors that enhance fungal adherence (Chaffin, 2008). In addition, *C. albicans* is capable of secreting metallopeptidases that break down essential proteins constituting the mucosal barrier, such as collagen, laminin, and fibronectin (Chaffin, 2008). Salivary components such as histatin, statherin, and Proline-Rich Proteins (PRPs) have been found to facilitate the anchoring of *C. albicans* to the implant surface (Johansson et al., 2000; O'Sullivan et al., 1997). Adhesins like Hwp1p, Saps, and the Als family of proteins have been identified as mediators for the binding of *C. albicans* to Buccal Epithelial Cells (BECs) (Albrecht et al., 2006; Chandra et al., 2001). Moreover, deletion of *Hwp1p, Als, Cry1,* and *SAPs* altered the adhesion properties of *C. albicans* to epithelial cells leading to reduced epithelial inflammation, reduced virulence and defective

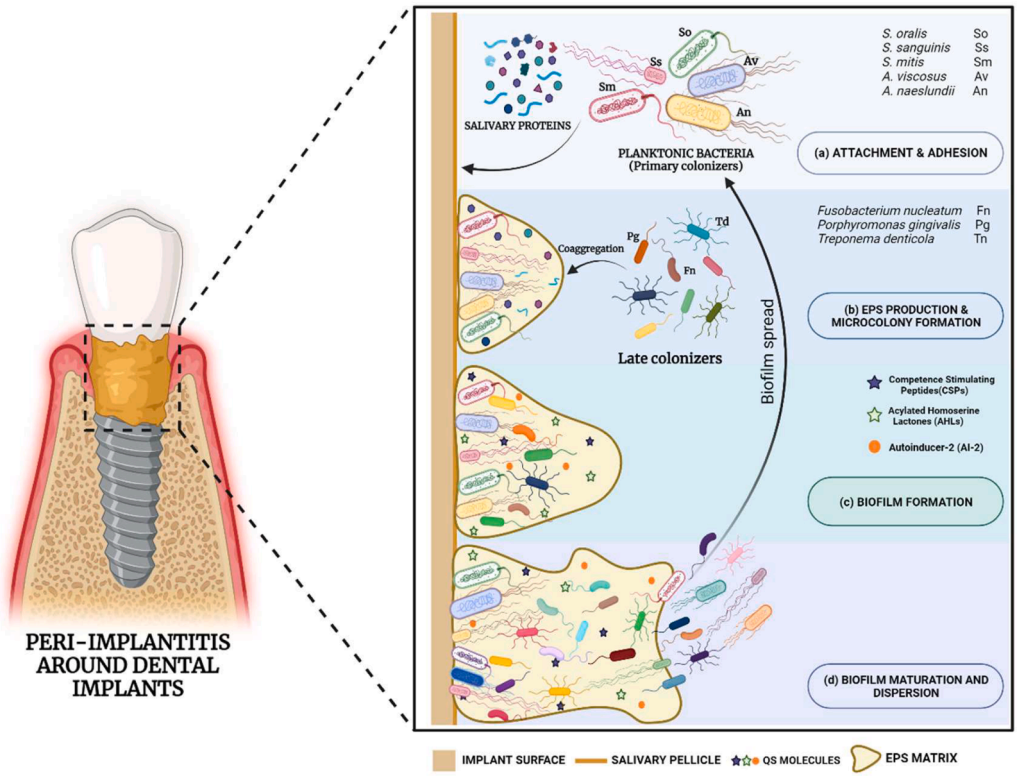

Fig. 1. Biofilms on dental implants: **(a)** Salivary proteins facilitate free-floating planktonic bacteria to attach to the implant surface, they form a reversible attachment using appendages like pili or fimbriae or by physical forces. **(b)** Attached bacteria secretes EPS that helps them adhere to each other and to the implant surface, forming an irreversible attachment. They then multiply and form microcolonies. **(c)** Quorum sensing is activated which enables cell-cell communication within the biofilm community, facilitating bacteria to further produce EPS, forming complex three-dimensional structures, the biofilm continues to grow and mature. **(d)** Some bacteria within the biofilm detach and disperse to colonize new implant surfaces aiding in biofilm spread and colonization. "Created with BioRender.com".

hyphal growth during experimental oral infection models (Ng et al., 2023; Nobbs et al., 2010). Furthermore, *C. albicans* transitions from its yeast to hyphae form within the biofilm, it secretes a pore-forming toxin, while cytolytic proteins and peptide toxins are well-known virulence factors in various bacterial pathogens, disrupting epithelial barriers and affecting cell function, these toxins were not previously identified in human pathogenic fungi. Therefore, the secreted toxins were first identified in opportunistic pathogen *C. albicans*, which directly damages epithelial membranes, activates emergency response signaling pathways, and stimulates epithelial immunity (Conti et al., 2016; Moyes et al., 2016).

Studies using phytochemicals revealed that *Eucalyptus globulus* (eucalyptus) and *Mentha piperita* (peppermint) oils reduced *C. albicans* biofilm formation by 80.87 % and 74.46 %, respectively. These oils not only effectively eliminated *C. albicans* cells but also hindered biofilm development (Agarwal et al., 2008). Leaves of *Bauhinia holophylla*, rich in flavonoids of the flavonol-3-O-glycoside type, exhibited effectiveness in inhibiting the development of *C. albicans* biofilms and the yeast-to-hyphae transition in vitro (Agarwal et al., 2008). Shikonin (SK) effectively suppressed *C. albicans* biofilms by preventing their formation and disrupting mature ones. *C. albicans* produces farnesol, when the concentration of farnesol reaches a certain threshold, it inhibits the transition from yeast to hyphae. SK was found to enhance farnesol production within *C. albicans* biofilms. Additionally, SK treatment markedly increased the expression of DPP3, a crucial gene in farnesol synthesis. Combining SK with farnesol significantly boosted their anti-biofilm activity compared to using SK alone (Yan et al., 2019).

3. Biofilms on orthopaedic implants and nanoparticles as antimicrobial compounds

Orthopaedic implants are versatile medical devices used for several applications such as soft tissue anchorage, joint replacement, deformity correction, and fracture fixation (Szczęsny et al., 2022). These implants are typically constructed from a range of materials including titanium, cobalt-chromium alloys, titanium alloys, stainless steel, polyethylene, alumina, zirconia, polymethylmethacrylate, and ceramics (Barber et al., 2021; Gibon et al., 2017; Mavrogenis et al., 2011; Szczęsny et al., 2022). For instance, hip implants are made of metals (titanium and cobalt alloys), ceramic materials (bioglasses, alumina, and calcium phosphates), high-density polyethylene and composite materials (polycarbonate carbon, polysulfone kevlar, and polycarbonate kevlar) (Aherwar et al., 2016). Spinal implants are made of stainless steel, titanium alloys, polyetherketone, and cobalt-chromium alloys (Eltorai et al., 2016; Kurtz and Devine, 2007). Porous orthopaedic implants are utilized to enhance osseointegration and bone tissue growth. The interconnected porous structures facilitate the infiltration and growth of host bone cells, leading to a strong connection between the implant and surrounding bones/tissues, ensuring stability and long-term fixation. Additionally, porous implants offer increased surface area, improved force distribution, enhanced biological activity including nutrient and oxygen exchange, and provide advantages in revision surgery (Carpenter et al., 2018; Matassi et al., 2013). Biofilm associated implant infections can have serious consequences including implant failure, paralysis, and even fatality (Simon and Fabry, 1991). This section explores biofilm-related orthopaedic implant failure. Osteomyelitis, discitis, epidural abscesses, prosthetic joint infection, and septic arthritis are some examples of diseases caused by biofilm formation on implants. It also discusses the material characteristics of orthopaedic implants in relation to biofilm

formation and outlines strategies to prevent implant failures.

Implant-related infections are commonly caused by various Gram-positive bacteria, including *S. aureus, S. epidermidis, Staphylococcus lugdunensis, S. viridans, Streptococcus agalactiae, Enterococcus faecium, and E. faecalis*. Additionally, Gram-negative bacteria such as *K. pneumoniae, E. coli, and P. aeruginosa* can also contribute to these infections (Arciola et al., 2018; Montanaro et al., 2011). Biofilm can be formed by single or multi-species and mechanisms for attachment and development of biofilm are discussed below (Montanaro et al., 2011; Otto, 2009). The orthopaedic implant is made of two distinct surfaces, abiotic surfaces and biotically coated surfaces (e.g.: coated with biotic coatings including cell and protein-based coatings. Abiotic coatings include hydroxyapatite coatings, titanium plasma spray coatings, antibacterial coatings, and drug-eluting coatings). The forces such as van der Waals, Lewis acid–base and electrostatic force facilitate the reversible attachment of bacteria to abiotic coated surfaces (Bos et al., 1999; Ribeiro et al., 2012). In addition, adhesins such as bacterial filamentous cell appendages, bacterial pili, cellulose nanofibers, and pilus-like adhesive structures promotes bacterial attachment to the implant surface (Speziale et al., 2009). Irreversible attachment of bacteria occurs predominantly in biotically coated implants when exposed to physiological fluids such as blood. Material surfaces are quickly covered by Extracellular Matrix (ECM) proteins that contain both bacterial proteins and host immune protein components (Speziale et al., 2009). The primary matrix proteins of orthopaedic implants that bind to bacterial adhesins include fibrinogen, fibronectins, and collagens which encourage bacterial adhesion on ECM (Campoccia et al., 2009). Cellular aggregation and EPS synthesis lead to colony development (Moormeier and Bayles, 2017). The colonies grow and get structured, forming mature biofilms (Le et al., 2014). The biofilm gets dispersed from the implant surface and diffuses into the blood causing systemic infections such as osteomyelitis (Arciola et al., 2018).

Osteomyelitis is a bone infection, which can be acute or chronic, caused by pyogenic organisms that enter the bone through the bloodstream, fractures, or surgical procedures (Huang et al., 2022). It results in inflammation, bone discomfort, and potential bone loss as the bacteria from the biofilm invade the surrounding bone tissue (Brady et al., 2008). The implant comes into contact with osteoblasts, which are bone-forming cells, as it is placed near host tissues/cells (Campoccia et al., 2016). These osteoblasts contribute to the formation of the Bone Extracellular Matrix (BEM), consisting of various structural proteins like collagen, sialoprotein, osteopontin, and fibronectin (Arciola et al., 2018). Bacteria attach to these BEM components using adhesins called Microbial Surface Components that Recognize Adhesive Matrix Molecules (MSCRAMMs) (Heilmann, 2011). While the host cells mount an immune response against the bacteria, the bacteria evade this response by hiding inside host cells, making them resistant to antibiotics and leukocytes. *S. aureus,* for example, utilizes the fibronectin bridge between osteoblasts and itself to enter osteoblasts (Fowler et al., 2000). This process involves the activation of Integrin-linked kinase (ILK) and Focal Adhesion Kinase (FAK), which modify the actin cytoskeleton and initiate bacterial internalization. The ILK-FAK pathway downstream of the α5β1 integrin receptor plays a crucial role in *S. aureus* internalization through endocytic uptake of the plasma membrane (Wang et al., 2020; Wen et al., 2020). Once inside osteoblasts, bacteria can undergo lysis by lysosomal enzymes or be enclosed in vesicles for protection. Following cell internalization, *S. aureus* may adopt a single colony variant (SCV) phenotype, characterized by high intracellular persistence and reduced antibiotic sensitivity (Hamza and Li, 2014). When *S. aureus* infects the osteoblast, it causes the release of cytokines. A type 2 membrane protein of the TNF superfamily, tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is released which stimulates apoptosis. In infected osteoblasts, DR4 and DR5 death receptors are expressed. Ligation of DR4 and DR5 is done by TRAIL to form a death-inducing signaling complex (DISC), which recruits caspase 8 and activation of caspase 3 causes apoptosis through an extrinsic pathway. Activation of apoptosis through intrinsic pathways through caspase 9 is also observed (Tummers and Green, 2017). *S. aureus* can induce osteoblast necrosis by producing virulent factors like phenol-soluble modulins (PSMs), which damage cell membranes. The presence of *S. aureus* within cells significantly diminishes osteoblast activity, leading to osteoblast necrosis and apoptosis, and results in the release of intracellular *S. aureus*, which can cause recurrent infection to other osteoblasts and encourage biofilm formation (Arciola et al., 2018; Josse et al., 2015). And ultimately resulting in bone loss and destruction, a condition known as osteomyelitis (Chen et al., 2014; Widaa et al., 2012; Young et al., 2011).

To prevent implant failure and reduce the risk of infection, various coating strategies are employed on the implant surface. These coatings include antibiotic, antiseptic, nano-silver, and photoactive-based coatings. Antibiotics such as gentamicin, amoxicillin, vancomycin, cephalothin, and tobramycin have been extensively studied for their effectiveness (Veerachamy et al., 2014). Antiseptic coatings such as chlorhexidine and chloroxylenol weaken bacterial adhesion and cause membrane damage (Cheung et al., 2012; Kim et al., 2013; Russell and Day, 1993). Chitosan, an antibacterial chitin polymer, is also used for its antibacterial properties (Yang et al., 2013). Nano-silver coatings demonstrate antibacterial activity, while photocatalyst coatings made of titanium oxide (TiO) have bactericidal effects when activated by UV (Kumaravel et al., 2021; Sondi and Salopek-Sondi, 2004). Non-coating technologies, such as antibiotic-loaded bone cement, antibiotic-loaded reservoirs, modified surface characteristics, electrospinning, and integrated biofilms (Integration of antimicrobial biofilms into the implant process), are also explored to combat bacterial infection in implants (Eltorai et al., 2016; Özçelik et al., 2015) (Table 3 and Fig. 2).

4. Biofilm on cochlear implants and phytochemicals as antimicrobial compounds

A cochlear implant (CI) is a neural prosthetic device used for treating hearing loss through electrical stimulation of the auditory nerve (Loizou, 1999). CI consists of two main components: an external sound processor worn behind the ear, and an internal implant surgically placed (Macherey and Carlyon, 2014). The implant surface, typically made of silicone, is susceptible to bacterial attachment and biofilm formation. Complications associated with cochlear implants primarily arise from surgical site issues (such as meningitis, cerebrospinal fluid leakage, and reparative granuloma) and device failure (Brown et al., 2009). Soft tissue infections, occurring in approximately 1.08 % of adults with CIs, are primarily caused by biofilm formation (Trinidade et al., 2008). Persistent infection and inflammation may contribute to device failure, which sometimes requires implant removal for proper healing (Im et al., 2015; Kempf et al., 1999). Additionally, biofilms can significantly contribute to skin flap issues during cochlear implant surgery (Kempf et al., 1999).

Common microorganisms found in biofilms on CIs include *S. aureus, Streptococcus pneumoniae* (*S. pneumoniae*), *P. aeruginosa, Streptococcus pyogenes, and S. epidermidis* (Kirchhoff et al., 2020). *P. aeruginosa* is particularly adept at colonizing implant surfaces within two weeks. The exact mechanism of biofilm formation on CIs is not fully understood, but it may involve polysaccharide-mediated or protein-mediated processes (Wang et al., 2004). In the case of *S. aureus*, the *ica*ABCD operon is responsible for producing polysaccharide intercellular adhesin during the later stages of infection, suggesting other factors contribute to the initial biofilm formation (Fluckiger et al., 2005). Biofilm commonly forms in the grooves of the CI, as well as along the magnet and between the magnet and silicone pocket. The rough and irregular surfaces of the magnet provide favorable conditions for bacterial attachment and biofilm formation (Vaid et al., 2013).

Post-operative cochlear implant infections can be managed with medications such as intravenous ceftriaxone, intravenous vancomycin, oral azithromycin, oral levofloxacin, and intravenous immunoglobulin to prevent the need for implant removal. Chronic infections in cochlear

Table 3
Potential antimicrobial coatings with bactericidal and biofilm inhibition activity for orthopaedic implants.

Substrate	Coating material	Susceptible species	Effect	Reference
Titanium	Poly(L-lysine)-grafted-poly (ethylene glycol) (PLL-*g*-PEG-RGD)	*S. epidermidis*, *S. mutans*, *P. aeruginosa*	Depending on the type of bacteria, bacterial adhesion decreased by a percentage of 88–98 % over the 24-h study.	(Maddikeri et al., 2008)
	Poly(*N*-isopropylacrylamide) (polyNIPAM)	*P. gingivalis, S. aureus*	Prevention of biofilm formation by detachment of bacteria from the implant surface.	(Xu et al., 2022)
	Hydrophobic polycation *N,N*-dodecyl, methyl-PEI -polyethylenimine	*S. aureus*	Prevents implant colonization and biofilm formation by cell lysis and promotes bone healing.	(Schaer et al., 2012)
	Gentamicin	*S. aureus*	Most efficient against biofilms of MRSA and MSSA. With the maturity of the biofilm, the needed antibiotic concentration rises.	(Okae et al., 2022)
	Doxycycline	*S. aureus*	Improved bone formation and reduced risk of infection around the implant	(Song et al., 2017)
	Chitosan	*S. aureus*	Compared to titanium untreated and chitosan coated titanium, MRSA biofilm development was reduced by up to 50 % and 75 %, respectively.	(Villegas et al., 2022)
	Silver ions	*P. gingivalis*	Reduced osteonecrosis by infectious osteomyelitis and elevation of the inflammatory factors like C-reactive protein and IL-6.	(Soma et al., 2022)
Cobalt-Chrome-Molybdenum (CoCrMo)	Titanium dioxide (TiO_2)	*S. aureus, E. coli*	Showed osteo differentiation potential and antibacterial activity without cytotoxicity	(D'Agostino et al., 2023)
Cobalt	Hydroxyapatite	*S. aureus*, *E. coli*	Enhanced angiogenesis and vascularization along with antimicrobial properties	(Bhattacharjee et al., 2020)
Stainless steel	Poly (ethylene glycol)-poly(propylene sulfide) (PEG-PPS)- vancomycin and tigecycline	*S. aureus, Propionibacterium acnes* (*P. acnes*), *S. epidermidis*	PEG-PPS-vancomycin had lower CFUs than PEG-PPS-tigecycline. (2.4×10^1, 8.5×10^1 CFUs, respectively)	(Hegde et al., 2020)

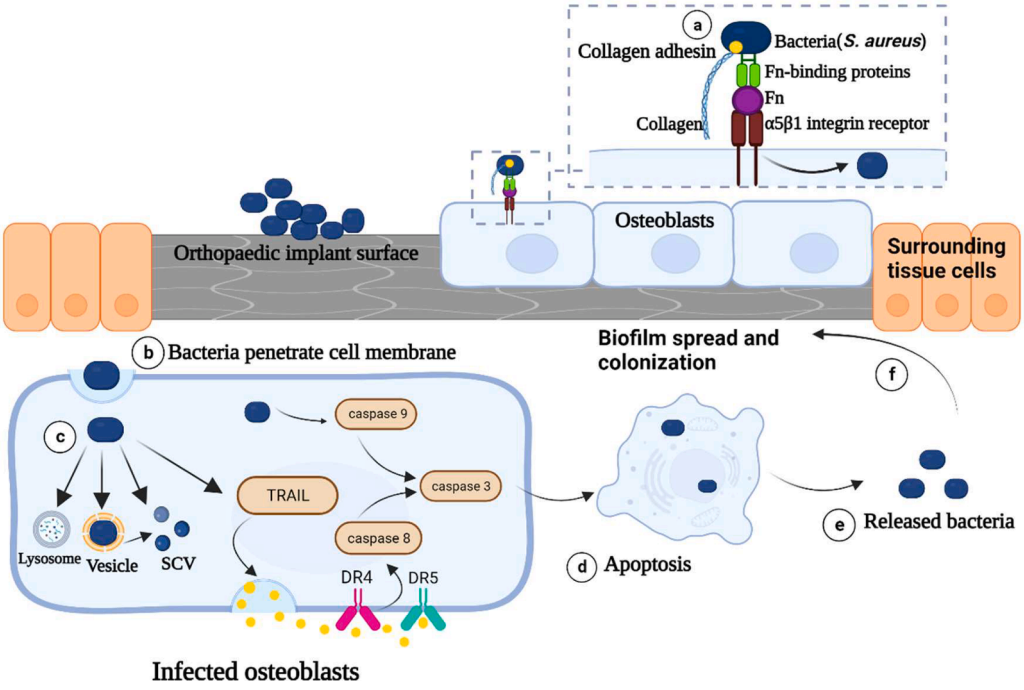

Fig. 2. Osteomyelitis caused by *S. aureus*: **(a)** Fibronectin-binding proteins of bacteria adhere to integrin receptors on osteoblasts via fibronectin, facilitating the binding of bacteria to collagen molecules on osteoblasts. **(b)** Bacteria establish binding with osteoblasts, allowing them to penetrate the cell membrane and evade host immune responses. **(c)** Bacteria present within osteoblasts may be destroyed by lysosomes, sequestered within vesicles, or form small colony variants. Additionally, bacterial infection triggers the production of cytokines (such as TRAIL), leading to the activation of death receptors and recruitment of caspase 3 for apoptosis. **(d)** Infected osteoblasts undergo apoptosis. **(e)** Bacteria are released from the osteoblasts. **(f)** Released bacteria disperse and infect other cells. "Created with BioRender.com".

implants are often associated with immunodeficiency (Yu et al., 2001). The administration of antibiotics like rifampicin has shown higher efficacy in treating biofilm-associated infections, particularly against *S. epidermidis* and Methicillin-resistant *Staphylococcus aureus* (MRSA) (Im et al., 2015). The use of absorbable gentamicin-impregnated collagen sheets has a bactericidal effect on Gram-positive bacteria, including *Staphylococci*, making it a potential adjunct treatment for soft tissue infections (Benito-González et al., 2014). Long-term, low-dose administration of clarithromycin (500 mg for 24 h in adults) has been found to inhibit protein synthesis and effectively kill *P. aeruginosa* (Garcia-Valdecasas, Jiménez-Moleon, Sainz, Fornieles, and Ballesteros, 2009). Terpinen-4-ol, an active component of *M. alternifolia*, an essential

oil, has shown susceptibility against biofilms formed by Methicillin-Susceptible *Staphylococcus aureus* (MSSA) and *P. aeruginosa* (Brady et al., 2010; Farnan et al., 2005). While conventional antimicrobials such as cefuroxime, gentamicin, rifampicin, and vancomycin have limited efficacy against *S. aureus* biofilms, recent research has indicated promising results with certain compounds. For example, a 5 % tea tree oil treatment for one hour effectively eradicated *S. aureus* biofilms on silicon implant surfaces (Brady et al., 2010). Sonochemical coating of ZnO or MgF_2 nanoparticles has been shown to reduce biofilm formation by strains of *S. pneumoniae* and *S. aureus* (Natan et al., 2016). The use of TiO_2 coating on silicone implants prevents initial bacterial attachment (Goldfinger et al., 2014). Cationic polymers containing quaternary ammonium salts (polyquats) exhibit broad-spectrum antimicrobial activity against fungi, Gram-positive, and Gram-negative bacteria (Kenawy et al., 2007). S53P4 BAG, composed of silicon dioxide, sodium oxide, calcium oxide, and phosphorus pentoxide, interferes with bacterial adhesion and possesses promising antibacterial properties. Treatment with synthetic BAG type S53P4 has been found to reduce EPS formation and create gaps in mature biofilms of *P. aeruginosa* (Kirchhoff et al., 2020). In addition to antimicrobial compounds, incorporating design modifications in cochlear implants, such as reducing surface depressions and utilizing titanium implants, has the potential to minimize bacterial adhesion and reduce biofilm formation (Pawlowski et al., 2005).

5. Biofilms on tracheal stents and silver nanoparticles as antimicrobial compounds

Trachea is a cartilaginous tube connecting the upper respiratory system and lungs. Tracheal damage can occur due to conditions like trauma, inflammation, tumors, or inborn abnormalities (Dhasmana et al., 2020). Tracheal stents, also known as airway tubes, are prostheses implanted through bronchoscopy procedures to treat airway diseases such as benign tumors, bronchial stenosis, and tracheobronchial compression (Folch and Keyes, 2018). Stents can be classified into covered (silicone, metallic, hybrid) and uncovered (expandable metallic) types (Folch and Keyes, 2018).

Granulation tissue plays a vital role in the process of wound healing, consisting of fibroblasts, macrophages, loose connective tissue, and newly developed capillaries. Granulation tissue associated with tracheobronchial tubes is colonized by various microorganisms such as *P. aeruginosa, S. aureus, S. viridans, C. albicans, Haemophilus influenzae* (Mazhar et al., 2014). The biofilm species is dependent on the implant material with silicone stents being rich in *Corynebacterium*-type biofilms. Similarly, *Staphylococcus* spp. is most commonly associated with covered metal stents (McGinniss et al., 2019). Biofilm accumulation seems to be more prominent in the distal parts of the tube and can be dispersed and moved to lungs (Perkins et al., 2010). Nasopharyngeal secretions containing oral bacteria flow through the trachea and collect at the ends of the tube where saliva facilitates bacterial adhesion. Saliva increases attachment to the poly-vinyl chloride (PVC) surface of the tube by increasing electrostatic interactions between bacterium and inert surface (Jones et al., 1997). Oral bacteria including *S. oralis, S. mitis* and *S. sanguis* are the primary colonizers. Viridans streptococci, specifically *S. gordonii*, are early colonizers and co-aggregate with a range of oral bacteria. Receptors which include mucins, agglutinins, proline-rich proteins, and enzymes such as alpha-amylase are recognized by primary colonizers. Salivary mucins like MUC5B, MUC7, gp340 have O-linked glycans that function as binding sites and enhance bacterial adhesion (Kindblom et al., 2012). *F. nucleatum*, acts as a mediator in the transition from early colonizers (*S. gordonii*) to late colonizers (*P. intermedia* and *T. denticola*). Nosocomial pathogens attach onto the oral biofilm formed, hence resulting in a complete biofilm structure. The different species present in the biofilm can have synergistic or antagonist interactions which can enhance virulence characteristics and antimicrobial resistance. *P. aeruginosa* virulence factors (like phospholipase C, type IV pili, and phenazines) have the potency to kill filamentous forms of *C. albicans* which then act as a source of nutrition for biofilm formation (Cairns et al., 2011).

Ventilator-Associated Pneumonia (VAP) is a frequent infection linked to the development of biofilms, with the presence of an endotracheal tube serving as a significant risk factor. The presence of an endotracheal tube interferes with the cough reflex and facilitates the buildup of mucus and secretions. This creates a direct route for pathogens and elevates the risk of infection (Cairns et al., 2011). Biofilm formation on the endotracheal tube can result in various complications, including partial tracheal obstruction, subglottic stenosis, bronchopulmonary dysplasia, postoperative bleeding, airway obstruction, and excessive wound contracture, leading to narrowing of the airway lumen (Mazhar et al., 2014; Vandecandelaere and Coenye, 2014) (Table 4 and Fig. 3).

6. Antimicrobial-derived compounds in mitigation of biofilms on central venous catheter

A Central Venous Catheter (CVC) is a medical instrument placed within veins including internal jugular, common femoral, subclavian, and other significant blood vessels to gain access to the central circulatory system. It serves various medical purposes, including administering medications, delivering fluids, facilitating total parenteral nutrition, blood transfusion, and assisting in complex procedures such as transvenous pacemaker placement (Kolikof et al., 2020). Occlusions in catheters are common, affecting 14–36 % of patients within the first two years following catheter insertion (Baskin et al., 2009). Thrombotic occlusion in a catheter occurs when a blood clot forms either inside the catheter's lumen or on the implant's surface (Wallace et al., 2017). Conversely, non-thrombotic occlusion can result from various factors, including the precipitation of medication, the buildup of lipid residues, or mechanical issues like external compression of the catheter (Montagnana et al., 2011). Prevalent complications linked with the utilization of CVCs are Catheter-related bloodstream infections (CRBSIs) and Catheter-related thrombosis (CRT). Once the CVC is in place, it encounters blood and the host proteins, including fibrin, fibrinogen, fibronectin, and platelets from the bloodstream, which begin to coat the catheter's surface (Lucas et al., 2014; May et al., 2015; Waters et al., 2022).

Fibrin sheaths develop within just 24 h of placing a CVC, and although there is a slight risk of potentially serious embolization, these events are typically symptom-free (Wallace et al., 2017). When bacteria infiltrate the system, they attach themselves to thrombosed blood and the blood proteins that coat the implant's surface. Once attached, these bacteria start to multiply, forming small clusters which eventually leads to formation of biofilms, resulting in production of EPS and maturation. Species such as *S. aureus, P. aeruginosa, E. coli*, and *S. epidermidis* are prominent biofilm formers on CVCs (Chauhan et al., 2016; Murga et al., 2001; Zandri et al., 2012). Bacteria residing within catheter biofilms can enter the bloodstream, resulting in CRBSIs (Yousif et al., 2015). In addition, these bacteria can adhere to heart valves, giving rise to infective endocarditis. In severe cases, when these microorganisms disseminate throughout the body, they can trigger sepsis, a condition that can harm tissues, impair organ function, and potentially lead to a fatal outcome (Donelli, 2006).

In order to prevent clot formation, catheters are coated with antithrombogenic agents such as poly-2-methoxyethylacrylate (PMEA). This preventive approach has also resulted in a decreased biofilm formation (Kariya et al., 2020; Sivakumar et al., 2023). Antimicrobial coatings such as the sulfadiazine-chlorhexidine and the minocycline-rifampin are applied onto CVCs to overcome bacterial accumulation, effectively targeting a wide range of pathogens (Aboulleish et al., 2021; Chatzinikolaou et al., 2003). Impregnated catheters are enriched with antimicrobials, such as silver ions or antimicrobial peptides, to combat infections and lower the risk of CRBSIs (Gominet

Table 4
Potential antimicrobial coatings for bactericidal and biofilm inhibition activity for tracheal stents.

Stent material	coating	Species studied	Effect	References
3D printed PPCA 8K-26-dA (Photo-curable acrylate triblock copolymers)	1 % w/w ciprofloxacin and Polyethylene glycol	*S. epidermidis, E. coli*	Prevents adhesion and fouling.	(Maity et al., 2021)
polycaprolactone fiber	Cisplatin and Ag NPs	*S. aureus, P. aeruginosa, C. albicans*	AgNPs bind with bacterial oxidation-reducing enzyme Q, react with bacterial nucleic acid and protein to inhibit bacterial proliferation and diffusion.	(Li et al., 2022)
Polylactic acid nanofiber membranes	Ag NPs	*S. aureus, P. aeruginosa*	Inhibition of bacterial adhesion, reduced biofilm thickness.	(Wang et al., 2017)
Carbon nanotubes	Ag NPs	*E. coli*	Loss of bacterial membrane integrity, irreversible damage to proteins, lipids and DNA, generation of reactive oxygen species which induce oxidative stress on bacteria.	(Wang et al., 2017)
Medical-grade PVC	NaOH/AgNO3	*P. aeruginosa*	cell death occurs at the biofilm–substratum interface, inhibition of bacterial adhesion.	(Balazs et al., 2004)

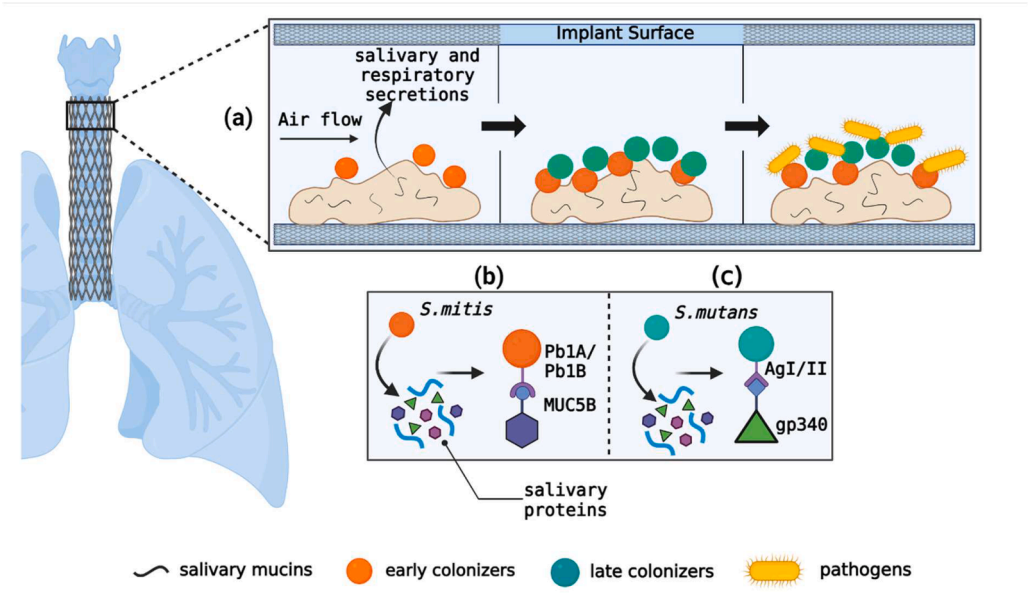

Fig. 3. Tracheal stents colonized by oral microbiota: **(a)** Salivary and respiratory secretions contain mucins that promote oral microbes adhesion, leading to biofilms formation. Mucins possess O-linked glycans with sialic acid residues, which enhance the initial attachment process. Early colonizers include *S. oralis, S. mitis* and *S. sanguinis* and late colonizers are *S. mutans, P. intermedia,* and *P. denticola.* **(b)** *S. mitis* recognize salivary proteins, such as MUC5B, through the receptor Pb1A/Pb1B. **(c)** Late colonizers like *S. mutans* possess Ag I/II receptors that can bind to low-density proteins such as MUC7, gp340, and IgA. "Created with BioRender.com".

et al., 2017; Maki et al., 1988). In a study, the application of Boron Carbon Nitride (BCN) nano-coatings to CVCs exhibited significant antimicrobial effects, resulting in a 75.52 % reduction in *Bacillus cereus* biofilm formation and a 62.13 % decrease in *E. coli* biofilm formation (Naga et al., 2020). Lock solution is a solution with antimicrobial and anticoagulant properties that are infused into the catheter lumen to prevent coagulation and biofilm formation. This includes the use of antibiotics like vancomycin, or alternatives like taurolidine-citrate and nitroglycerine (Chaftari et al., 2017; Chong et al., 2020; Naga et al., 2020; Ranch-Lundin et al., 2021). Typically, high concentrations of active agents are used in lock solution to effectively combat the source of CRBSIs caused by biofilms, increasing the safety and efficiency of catheter applications in healthcare settings (Snaterse et al., 2010). Peripherally inserted central catheters (PICCs) are a safer alternative of CVCs for medium to long-term therapy due to their less invasive technique, lower mechanical complications, and likely reduced infection rates. Although infections associated with PICC lines can occur, the risk of bloodstream infections is not higher when compared to traditional central catheters (Pitiriga et al., 2022) (Fig. 4).

7. Antimicrobial irrigation on breast implants to eradicate biofilm formation

Silicone or saline-filled silicone breast implants are employed in procedures such as breast augmentation and breast reconstruction following mastectomy (Rieger et al., 2013). Complications associated with biofilms in breast implants encompass capsular contracture, Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BI-ALCL), double-capsule formation, infections, and altered nipple sensation. These issues arise in approximately 1.5–2.5 % of cosmetic cases and 20–35 % of reconstructive surgeries involving breast implants (Brindle et al., 2018; James et al., 2019). The progression in development of biofilm can result in persistent inflammation, the development of capsular fibrosis, and ultimately, the onset of capsular contracture. Capsular contracture, a prevalent problem affecting approximately 30 % of patients, includes the contraction of the collagen capsule that naturally develops around the implant, leading to discomfort and distortion in shape (Ajdic et al., 2016; Rieger et al., 2013). The microflora inhabiting the skin and breast ducts can irreversibly adhere to the implant's surface and might be introduced during surgical procedures (Rieger et al., 2013). Common bacteria associated with breast implant-related infections comprise Coagulase-negative *staphylococci, S. epidermidis*,

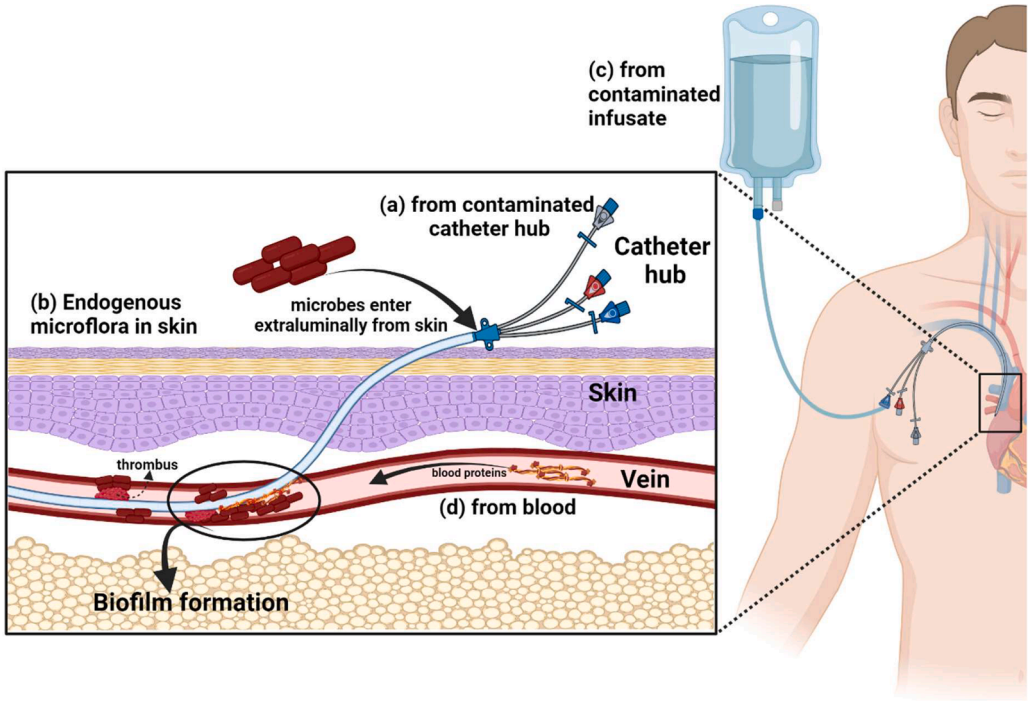

Fig. 4. Sources of bacterial contamination and biofilm formation on CVCs: **(a)** Catheter hub contamination: Improper disinfection or contaminated catheter hubs facilitate bacterial colonization. During fluid administration, these bacteria migrate along the catheter lumen and establish biofilms. **(b)** Skin flora: Despite usage of antiseptic techniques during CVC placement, residual skin microbes colonize the insertion site and adhere to catheter surface. **(c)** Infusate contamination: During the preparation, storage, and administration phases, the sterility of the infusate can be affected. Introduction of such infusates into CVC lumen can lead to bacterial colonization. **(d)** Internal catheter environment after bacterial colonization: Presence of blood proteins such as fibrin, fibrinogen, fibronectin, and platelets and thrombus (blood clot) provide favourable attachment sites for bacterial colonization and proliferation within the catheter lumen and on the surface of catheter. Biofilms mature and spread in the system through blood causing CRBSIs. "Created with BioRender.com".

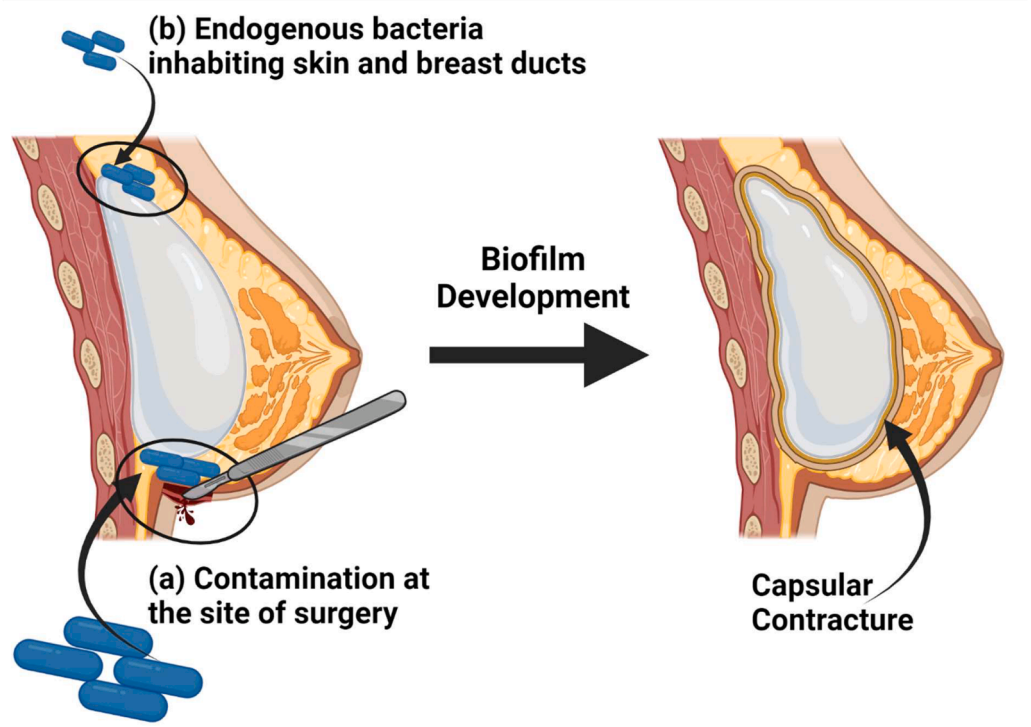

Fig. 5. Biofilm development on silicone breast implants leading to capsular contracture: **(a)** Bacterial species can contaminate implant surface during surgery procedures. **(b)** Microflora of the skin or breast ducts (Propionibacterium, Corynebacterium spp.) can form biofilm on implant surface. Bacterial biofilm formation leads to local inflammation, capsular fibrosis and then capsular contracture. Capsular contracture causes pain and implant distortion. Created with BioRender.com".

MRSA, *P. acnes*, Corynebacterium, and Lactobacilli (Ajdic et al., 2016; Pittet et al., 2005).

The systemic administration of cephalosporin, prior to surgery and extending for up to one week following implantation, along with immersing the implant in an antiseptic or antibiotic solution (such as cephalosporin, bacitracin, or neosporin) has demonstrated potential for reducing the incidence of infections (Pittet et al., 2005). To avoid complications such as capsular contracture, physicians often employ antimicrobial irrigation within the breast pocket or around the implant (Awad et al., 2022). Breast pocket irrigation with antibacterials such as betadine, gentamicin, and cefazolin solution has been effective in preventing biofilm formation. Chloramex, Fucidin, and Terramycin coated disks effectively suppressed biofilm formation by *S. epidermidis* for at least seven days (van Heerden, Turner, Hoffmann, and Moolman, 2009). Polypropylene mesh discs infused with antibiotics and coated with a minocycline and rifampicin-carrying polymer exhibited reduced biofilm formation compared to untreated implants (Jacombs et al., 2012) (Fig. 5).

8. Physical and chemical treatment on hemodialyzer to mitigate biofilm formation

The hemodialyzer, often referred to as an artificial kidney, is a medical device employed for blood purification. During the dialysis process, blood circulates in close proximity to a semi-permeable membrane, known as the dialyzer, and a solution containing mineral salts, referred to as the dialysate. Bacterial colonization on the outer surface of catheters used in dialysis occurs due to contact with hands engaged in catheter manipulation or proximity to the skin around the catheter hub. Inside hemodialyzers, the fluid pathways serve as entry points for bacteria, and when combined with organic components from dialysis fluid and water, they create a favourable environment for bacterial biofilm growth (Dasgupta, 2002). The endotoxins associated with these biofilms can provoke pyrogenic reactions in patients, potentially leading to persistent conditions like chronic cardiovascular and joint disorders, as well as carpal tunnel syndrome (Cappelli et al., 2005; Marion-Ferey et al., 2003). Bloodstream infections (BSIs) primarily result from dialyzer reuse, and each additional use raises the BSI risk by 7 % (Edens et al., 2017). Common biofilm forming species include *Burkholderia cepacia,* and *Stenotrophomonas maltophilia*, typically found within the silicone tubing of dialysis equipment. The rough inner surface of dialysis systems, combined with the presence of sodium and magnesium carbonate crystals, enhance bacterial adhesion and proliferation (Marion-Ferey et al., 2003). Combined use of citric acid and heat disinfection could be effective in removing *P. aeruginosa* biofilms in hydraulic circuit of haemodialysis machines (Holmes et al., 2004) (Fig. 6).

9. Antimicrobial coating on urinary catheters

Urinary catheters are made either from silicone or latex which comprise of a pliable tube that is inserted through the urethra into the bladder. Urinary tract infections (UTIs) are prevalent in hospital settings, with Catheter-associated Urinary Tract Infections (CAUTIs) accounting for 70–80 % of these cases. Roughly 25 % of hospital patients receive a urinary catheter, increasing CAUTI risk (Clarke et al., 2020). UTIs are caused by Gram-positive bacteria (e.g., *E. faecalis, S. aureus*, group B *Streptococcus* (GBS)), Gram-negative bacteria (e.g., *E. coli, K. Pneumonia, Proteus mirabilis* (*P. Mirabilis*), *P. aeruginosa*), as well as some fungal species (e.g., *Candida* spp.) (Flores-Mireles et al., 2015; Govindarajan et al., 2022; Jacobsen and Shirtliff, 2011). UTI starts when uropathogens from the gut or bacteria from the skin around the urethral opening migrate to the urethra and then progress to the bladder. The conditioned biofilms comprise of components from urine and host proteins (eg: fibrinogen) on catheter surface supports bacterial adhesion (e.g., Ace adhesin in *E. faecalis* and TaaP adhesin in *P. mirabilis*). Such bacterial surface proteins recognize receptors on bladder epithelium.

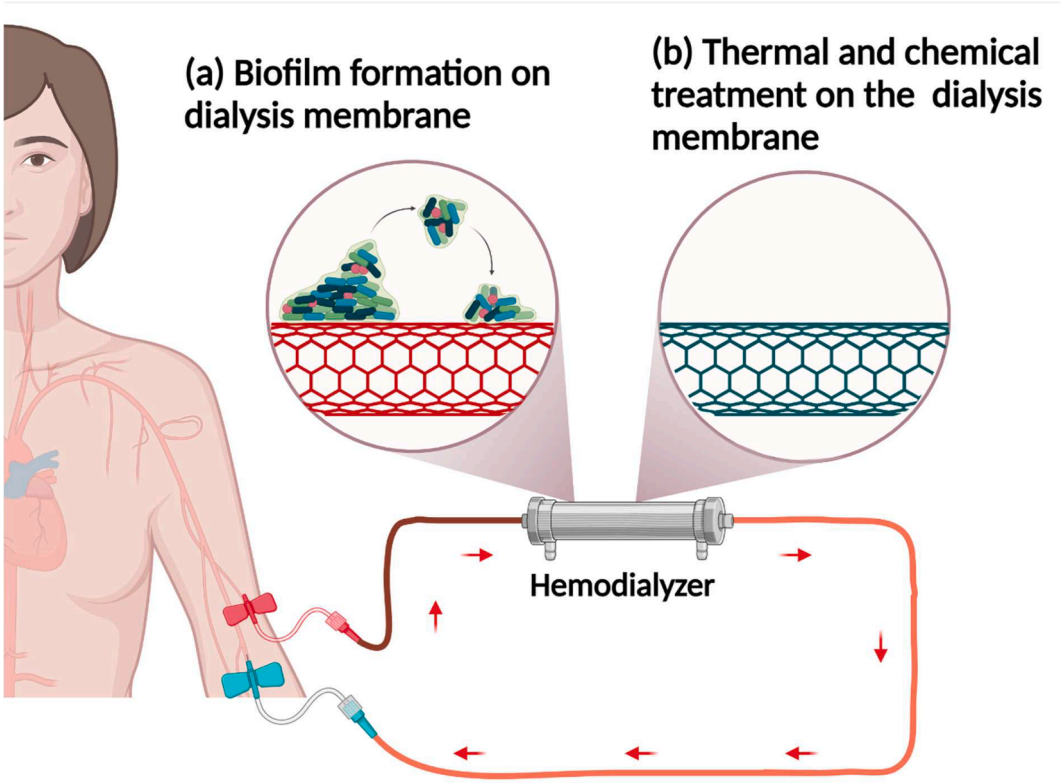

Fig. 6. Blood-stream infections caused due to reuse of hemodialyzer: **(a)** Biofilm formation on the membrane of hemodialyzer is promoted by organic substances present in the dialysis fluid. **(b)** Thermal and chemical treatment is necessary to remove biofilm formation on membrane surface before each reuse. "Created with BioRender.com".

Bacteria produce toxins such as hemolysins (e.g., *P. mirabilis*) that damage host cells and subsequently the uropathogens colonise the kidney. One significant complication linked to prolonged catheterization is the development of crystalline biofilms, primarily caused by bacterial species that produce urease. An unusual crystalline biofilm is formed by *P. aeruginosa* that can lead to catheter encrustation and blockage (Flores-Mireles et al., 2015; Meganathan et al., 2024; Pelling et al., 2019).

Common antimicrobial strategies used for catheters include coating of catheters (with antibiotics, nanoparticles, hydrogels, polytetrafluoroethylene) and use of antifouling agents (PEG, topographic surfaces, biosurfactants, and zwitterionic polymers) (Zhang et al., 2019; Zhu et al., 2019). When superhydrophobic surfaces come in contact with water, they have the capacity to capture air within their micro/-nanostructures that inhibits colonization of bacteria (Zhang et al., 2013). A superhydrophobic coating comprising polydopamine (PDA) layers and hydrophobically modified silver nanoparticles (AgNPs) reduced the adhesion of *E. coli* and *P. mirabilis* by 96.1 % and 84.9 %, respectively, compared to untreated silicone catheters (Zhang et al., 2019). Diamond Like Carbon (DLC) coating of the lumen of silicon catheter hinders the twitching motility and subsequent formation of microcolonies by *P. aeruginosa* expressing Green Fluorescent Protein (GFP). Twitching motility, facilitated by Type IV pili, plays a pivotal role in promoting interactions between cells, interactions with non-living surfaces, and the migration of cells to form aggregates (O'Toole and Kolter, 1998; Watari et al., 2021). The use of Tannic acid (TA) and copper ion coated catheter resulted in killing of more than 97 % of *P. mirabilis* and more than 99 % of *E. coli* and *S. aureus* due to the synergistic antibacterial effect of TA and copper ions (Huang et al., 2022). Sonohemical coating of ZnO nanoparticles and biofilm matrix degrading amylase on silicone catheters inhibited biofilm formation up to 70 % by amylase induced degradation of bacterial adhesives (Ivanova et al., 2021). Antimicrobial peptides such as Human-β-defensin−3, Nisin A, and Hepcidin-20 have the capability to inhibit the initial adhesion of bacteria, disrupt mature biofilms through detachment or bacterial killing, and target the EPS within biofilms (Bharadwaj et al., 2021). Using the CRISPR/Cas9-HDR approach, the knockout of genes involved in quorum sensing (*luxS*) as well as adhesion (*fimH* and *bolA*) led to weakened and reduced biofilm formation. In particular, the mutant strains Δ*luxS*, Δ*fimH*, and Δ*bolA* exhibited lower biofilm formation on urinary catheters when compared to wild-type strains of *E. coli* (Alshammari et al., 2023). *Eucalyptus camaldulensis*-mediated synthesized silver nanoparticles reduces bacterial adhesion of *E. coli* and *S. aureus* due to repulsion between AgNPs and bacterial surface proteins (Lethongkam et al., 2022).

10. Biofilms on intraocular lenses, heart valves, and pacemakers

In cataract surgery, Intra-Ocular Lenses (IOLs) are utilized to mimic the refractive capabilities of the natural crystalline lens. There are two types of IOLs: single-piece lenses composed entirely of the same material, and multi-piece lenses with distinct materials for the haptic and optic parts (Werner, 2021). Polymers such as acrylic or silicone, are commonly employed for IOL manufacturing. Multifocal IOLs have the ability to diffract and refract light simultaneously, allowing for clear vision at both near and distant distances (Alio et al., 2017).

Postoperative Endophthalmitis (PE) is a condition characterized by inflammation of the posterior eye and is commonly associated with biofilm infections. The primary causative agents of PE are ocular microbiota, particularly Coagulase-negative *Staphylococci* (CoNS), such as *S. epidermidis*. Other bacteria like *P. acnes, Corynebacterium* spp., and *S. aureus* can also contribute to PE (Bispo et al., 2015; Mazoteras and Casaroli-Marano, 2015). The formation of biofilms on IOLs depends on the implant material and the presence of specific genes, such as the *ica* locus. Notably, *S. epidermidis* shows the highest adherence to silicone polymers and the lowest adherence to hydrophilic acrylic polymers (Baillif et al., 2008). *S. epidermidis* strains that possess the *ica* locus exhibit an enhanced capacity to develop strong biofilms (Bispo et al., 2015).

An acrylic IOL composed of poly (2-phenoxyethyl methacrylate-co-2-phenoxyethyl acrylate-co-2-ethylhexyl methacrylate), with a polydopamine coating followed by gentamicin conjugation, exhibited a significant 74 % decrease in bacterial adhesion, particularly in the case of *S. aureus* (Xiang et al., 2021). Additionally, a hyaluronic acid-lysozyme (HA-lysozyme) composite coating on a Poly-methyl methacrylate on IOL created a highly hydrophilic surface, which exhibited anti-adhesive properties against *S. aureus* (Wang et al., 2015).

Artificial heart valve implants are utilized as substitutes for dysfunctional heart valves resulting from valvular heart diseases, such as aortic valve disease, particularly aortic stenosis. These implants can be classified into three main groups: mechanical heart valves, bioprosthetic tissue valves, polymeric valves, and engineered tissue valves (Singhal et al., 2013).

Various bacterial species, including *S. aureus, S. mutans, P. aeruginosa, E. coli, E. faecalis, K. pneumoniae, S. epidermidis, Acinetobacter baumannii, Enterobacter cloacae* (*E. cloacae*), and *Enterobacter aerogenes* (*E. aerogenes*), can contribute to biofilm-associated infections on heart valve implants (Viola and Darouiche, 2011). Some key factors that influence the attachment and formation of biofilms are surface characteristics of the implants, blood flow and shear forces, and the formation of conditioning films due to body fluids (such as blood). The presence of circulating platelets and fibrin can trigger the aggregation and injury of tissue, ultimately leading to the formation of fibrin clots. These areas are more susceptible to colonization by microorganisms, leading to complications such as infective endocarditis, prosthetic valve endocarditis, valve degeneration, chronic inflammation, and thromboembolism (Viola and Darouiche, 2011).

Prevention of mechanical valve thrombosis can be achieved by employing a catechol-based method to develop a drug-releasing multilayer coating that adheres to mechanical valves (Lancellotti et al., 2023). Studies have demonstrated the antibacterial effect and cytotoxicity of titanium and titanium dioxide, which can effectively prevent periprosthetic infections (Norambuena et al., 2017). Hydrophobic coatings like polyacrylic acid and polydimethylsiloxane have shown anti-biofouling activity by inhibiting bacterial adherence and reducing biofilm formation through surface attachment reduction (Lei et al., 2021). Covalently coupled cross-linked nanogels with polyethylene glycol have been utilized to release ticagrelor and minocycline, effectively preventing thrombosis (Lancellotti et al., 2023). Antibiotic coatings incorporating vancomycin, daptomycin, minocycline, and rifampin have also been incorporated into various coatings (Guleri et al., 2017). Natural polymers such as Chitosan are utilized for their antimicrobial properties (Fu et al., 2017), while quaternary ammonium compounds, prevent the adhesion of microorganisms, thus inhibiting biofilm formation (Kula et al., 2022).

A pacemaker is a medical device used to regulate a slower-than-usual heart rate, commonly seen in conditions such as heart arrhythmia. Various materials, including titanium, stainless steel, ceramic materials (such as alumina or zirconia), platinum, polyurethane, and silicone, are employed in the design of pacemakers. These materials provide the necessary properties for the device's functionality and compatibility within the body (Mallela et al., 2004).

Biofilms in pacemakers are predominantly caused by bacteria such as MRSA, MSSA, methicillin-resistant *S. epidermidis* (MRSE), and methicillin-sensitive *S. epidermidis* (MSSE) (Fakhro et al., 2016; Santos et al., 2011). Other Gram-positive species like *E. faecalis, E. cloacae, E. aerogenes*, and Gram-negative species including *P. aeruginosa, Corynebacterium amycolatum* (*C. amycolatum*), and *K. pneumoniae* can also form biofilms on pacemakers. These microorganisms enter the bloodstream and adhere to the pacemaker's surface, leading to the development of biofilms (Rodriguez et al., 2013; Sohail et al., 2007; Tarakji et al., 2010). The presence of biofilms can cause clinical indications of infection, such as swelling and redness in the area surrounding the pacemaker site or

within the pacemaker pocket (Döring et al., 2018). Additionally, other diseases such as sepsis, pneumonia, and abscess formation are caused by biofilms (Caldara et al., 2022; Cámara et al., 2022; Freedman et al., 2020).

Currently, various antimicrobial coatings, including antibiotics like vancomycin, cefuroxime, and daptomycin, are being utilized in the field of pacemakers. For instance, nebacetin coated on titan platelets has demonstrated effective in vitro antibacterial efficacy against infections caused by both Gram-positive and Gram-negative bacteria (Marsch et al., 2014). Another promising approach involves employing Graphene Oxide (GO) nanoparticles, which exhibit antibacterial activity by inducing oxidative stress and physically trapping bacteria within aggregated nanosheets. This leads to the suffocation of bacterial cells and thus hinders their proliferation. Additionally, the agluna antimicrobial surface, containing silver ions, has been shown to inhibit local bacterial colonization (Shawcross et al., 2017; Yadav et al., 2017). In the context of pacemakers, the Micra transcatheter pacemaker, encased in titanium with a parylene coating, has shown reduced bacterial adhesion for *S. aureus* and *P. aeruginosa.* These antimicrobial coatings and surface modifications hold promise for enhancing the infection resistance of pacemakers and improving patient outcomes (El-Chami et al., 2020).

11. Conclusions

In recent years implants with an antimicrobial coating (eg, antibiotics, nanoparticles, and antiseptics) have shown promising results in reducing implant failure (Knetsch and Koole, 2011). Researchers are actively exploring non-antibiotic antimicrobial coatings as a potential solution to address the problems with emerging drug-resistant pathogens (Raza et al., 2021). Such coating strategies take advantage of nanoparticles, metallic and metal oxide materials, Photo-Dynamic Treatment (PDT), surface modifications, and antimicrobial peptides (AMPs) to inhibit bacterial growth (Huo et al., 2021). Each of these coating systems offers unique benefits with some pitfalls that require careful consideration in their application. In the field of orthopedic implants, the CVDVP200 coating, which involves the deposition of tantalum on the implant surface, has demonstrated anti-corrosion, antimicrobial properties, improved cellular adhesion compared to titanium, and enhanced wear resistance for joint applications (Wang et al., 2021). However, the fabrication process is complex and expensive. Another example is Roxolid, a high-performance alloy (for dental applications) developed by Straumann (a Swiss-based manufacturer of dental implants) which consists of 15 % zirconium and 85 % titanium and features a titanium plasma-spray surface. Roxolid exhibits good osseointegration ability and high tensile strength, making it a favorable option for dental implants. Continued research and development in the field of implant coatings are essential to optimize their performance, enhance antimicrobial properties, and overcome any limitations associated with their fabrication and cost.

The application of phytochemicals and other non-antibiotic compounds to address biofilm formation on medical implants is currently limited by a lack of scientific evidence regarding their efficacy, potential side effects, optimal dosage, and long-term impacts (Braem et al., 2023). Further research is necessary to understand important factors such as cytotoxicity, stability of compounds in biological fluids, and overall effectiveness in combating biofilm-related challenges (De Avila et al., 2022). Additionally, targeting specific signaling molecules involved in the QS system of bacteria using QS blockers have shown promising results in biofilm control (Brackman and Coenye, 2015). However, the majority of biofilms consist of diverse bacterial species with different QS mechanisms and signaling molecules, making it challenging to develop QS blockers that effectively target multiple types of bacteria (Roy et al., 2011). Furthermore, continuous exposure to QS blockers carries the risk of bacterial strains developing resistance to their inhibitory effects. Therefore, a comprehensive understanding of these compounds and their potential limitations is essential for their successful implementation in combating biofilms-associated implant failures (K Bhardwaj, Vinothkumar, and Rajpara, 2013).

Future research should also focus on the advancement of antimicrobial coatings that efficiently prevent microbial growth on implant surfaces, thereby reducing the potential for infections (Wei et al., 2019). It is also important to focus on creating coatings that exhibit long-lasting antimicrobial effects and sustained protection against bacterial infection (Kim et al., 2021). Given the emergence of drug-resistant bacterial strains due to excessive antibiotic use, it is crucial to develop diverse strategies, such as alternative non-antibiotic antimicrobial agents or combination therapies as this will improve treatment efficacy and reduce surgical revisions.

CRediT authorship contribution statement

Lohita Kadirvelu: Conceptualization, Data curation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sowmiya Sri Sivaramalingam:** Conceptualization, Data curation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Deepsikha Jothivel:** Conceptualization, Data curation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Dhivia Dharshika Chithiraiselvan:** Conceptualization, Data curation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Deenadayalan Karaiyagowder Govindarajan:** Conceptualization, Data curation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Kumaravel Kandaswamy:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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