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REVIEW ARTICLE

Candida albicans Impact on the Progression, Morphology, and Cellular Integrity of Biofilm Formation on the Surfaces of Implants; Current Knowledge and Future Perspectives

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ABSTRACT

The capacity of *Candida albicans* to adhere to diverse oral substrates constitutes a pivotal preliminary phase in the formation of a pathogenic fungal biofilm. Yeast cells demonstrate a considerable ability to bind to host tissues, encompassing dental structures and mucosal surfaces, in addition to synthetic, non-biological materials such as dental appliances. Biomaterials utilized for the restoration of oral functionality are prone to biofilm formation, which can detrimentally affect oral health. Oral microorganisms can adhere to both hydrophobic and hydrophilic surfaces; however, in vivo investigations indicate that hydrophobic surfaces tend to accumulate minimal biofilm due to differential shear forces. Rough surfaces are observed to retain more biofilm compared to their smooth counterparts. The presence of biofilms on composite materials and glass-ionomer cement types results in surface degradation, consequently fostering additional biofilm development. While the leaching of residual monomers from composites has been shown to influence biofilm proliferation in vitro, the effect in vivo appears to be less consequential, likely attributable to the dilution and continual renewal of saliva. Furthermore, research has produced inconsistent findings regarding the influence of fluoride release from glass-ionomer cement types. A comparative analysis is conducted between biomaterial-associated infections in implants and devices situated in other anatomical regions and the formation of oral biofilms. The discourse critically evaluates alterations to biomaterials aimed at diminishing biofilm formation on implants and devices, taking into account their prospective applications within dentistry. The conclusion reached is that for dental applications, antimicrobial coatings that exterminate fungi upon contact are deemed more efficacious than those that gradually release antimicrobial agents.

Keywords: Biofilm, *Candidia albicans*, Implant

Introduction

Biofilms constitute intricate and multifaceted assemblages of microorganisms that are securely affixed to diverse surfaces of implanted medical apparatus, and these assemblages are enveloped within a resilient and dense extracellular matrix that affords both protection and structural stability to the microorganisms contained therein (1). Importantly, it is estimated that approximately 65% of all microbial infections affecting humans are linked to the development of biofilms, underscoring the substantial prevalence and significance of this phenomenon in medical contexts. Therefore, investigating the role of these biofilms, identifying their compositional characteristics, and evaluating the implications of microbial biofilms on the effectiveness of human medical therapies represent a highly valuable and compelling domain of scholarly research (2). The microorganisms residing within these biofilms, which encompass various species of fungi and bacteria, demonstrate an extraordinary level of insensitivity or diminished sensitivity to antimicrobial agents, thereby complicating therapeutic interventions and prolonging the duration of infections.

This distinctive attribute of microorganisms, which allows them to adhere firmly to a wide range of surfaces, is pivotal in promoting the formation of biofilms in clinical settings, such as in the instances of indwelling catheters, prosthetic heart valves, joints, dental implants, and various tissues within the host organism, ultimately resulting in effective colonization and the subsequent emergence of drug-resistant infections (2, 3). Oral candidiasis (OC) is an opportunistic infection that affects the oral mucosa. It is caused by a rise in virulence of normally innocuous yeasts from the *Candida* species under conditions that are both systemic and locally predisposing. Notably, the two main local characteristics that predispose people to an increased risk of OC are xerostomia and dirty dental prostheses, especially in the elderly and those who wear dentures (4). The age of the patient (particularly in young people and people over 65), harmful behaviors (such as smoking and poor dental hygiene), syndromic or genetic disorders, iatrogenic factors (such as steroids, immunosuppressants, and broad-spectrum antibiotic therapy), and long-term systemic illnesses (like diabetes mellitus and immune deficiencies) are the main extraneous conditions that are associated with this condition (4, 5). In the 1940s, a spiral stainless-steel implant was created to promote bone growth on metal surfaces, which later advanced into a double-helical spiral design. Notably, in 1965, Dr. Per-Ingvar Brånemark introduced a threaded titanium root-form implant, marking the first well-documented stable dental implant used in patients (6, 7). Since that period, dental implants have undergone considerable advancements regarding their morphology, dimensions, and surface properties to improve their longevity and efficacy rates. Simultaneously, specific parameters have been delineated to objectively evaluate implant success, which encompass elements such as stability, the lack of peri-implant radiolucency, marginal bone resorption of less than 1 mm during the initial year of function and 0.2 mm per year subsequently, a width of attached gingiva exceeding 2 mm, and the absence of discomfort, infection, paresthesia, or other neuropathic conditions, alongside the procedure being executed without adverse events (6, 8).

The initial phase of osseointegration is recognized as primary stability, which is established during the surgical placement of the implant. As the healing process progresses and new bone forms, secondary stability is attained. It is crucial to note that both phases of osseointegration can be affected by the characteristics of the implant (9). Specifically, the implant surface, which is in direct contact with the biological environment, significantly influences the biological response and the mechanical strength of the interaction between the implant and surrounding tissue, thereby playing a vital role in determining the implant's short- and long-term outcomes. For example, surface texturing enhances the surface area, allowing for better stress distribution and facilitating direct contact between bone and implant (10). Additionally, surface properties that influence molecular interactions, cellular responses, and bone regeneration are critical to the success of the implantation process. Surfaces that promote osteoblast growth and the production of growth factors and cytokines will have a favorable impact on osseointegration (9, 11).

Osseointegration can be viewed as a contest between infectious organisms that aim to contaminate, colonize, and form biofilms on the implant surface, and the body's endogenous tissues that strive to integrate with the implants through osteogenesis (6). Consequently, the most prevalent complications associated with

implants often arise at the implant-bone interface. Peri-implantitis, a chronic inflammation related to biofilm formation and mediated by the immune system, affects the sites of the implants and is marked by the loss of supporting bone (12). Similar to the biofilm development on natural teeth, bacterial colonization begins within minutes following the implantation procedure and continues throughout the implant's lifespan. The buildup of biofilm and particular anaerobic pathogens are recognized as the main causes of bone loss. For more than ten years, peri-implantitis has been addressed through mechanical debridement and the use of antimicrobials typically employed for treating periodontitis, a gum disease affecting natural teeth. This condition shares similar characteristics, such as biofilm formation, indications of soft tissue inflammation, greater probing depth and bleeding in the gingival pocket, as well as the deterioration of supporting bone structures (1).

Adhesion plays a critical role in the processes of colonization and infection, making it a key factor in the pathogenesis of various diseases associated with C. albicans. Research indicates that the initial phase of numerous microbial infections is characterized by the adherence of microorganisms to specific target tissues (13). It is crucial to understand how biofilms may be affected by the materials used in implants, as microorganisms that attach to these materials can spread to other oral surfaces, potentially leading to infections in susceptible individuals. Consequently, investigations into the adhesion of C. albicans to biomaterials have primarily concentrated on denture bases and relining materials, although fungi are known to effectively adhere to a wide range of surfaces, including resin, glass, and metal (14).

Validated biofilm models have been used to study microorganism interactions and evaluate in vivo and in vitro treatments. Findings indicate that C. albicans influences biofilm structure and enhances the virulence of specific periodontal pathogens. However, the overall impact of *C. albicans* on multispecies biofilms or its role in biofilm formation on dental implant surfaces remains understudied. This review aims to examine the effects of *C. albicans* on the development, kinetics, structure, and viability of biofilms on dental implant surfaces, along with the associated immune responses. Understanding these interactions may aid in creating new therapies for managing periodontal and peri-implant diseases. Additionally, this study seeks to clarify the surface characteristics, progression, and morphology of various restorative materials for implant overdentures while evaluating the initial adhesion and cellular mechanisms of C. albicans biofilm formation on these surfaces.

Literature Search and Selection

A narrative review of the literature on the context of oropharyngeal candidiasis (OPC) in the biofilm formation on the surface of implants was carried out. Inclusion criteria encompassed articles written in English, available in full-text format, comprehensive, and directly relevant to the subject matter under investigation. A thorough search was conducted in PubMed and Scopus databases in December 2024, utilizing keywords associated with OPC / OC, oropharyngeal candidiasis, *Candida albicans*, candida biofilm, biofilm, and dental implant or implant. From the initial search, 145 articles were retrieved based on their titles, abstracts, and publication dates. After eliminating duplicate entries, a total of 72 distinct articles remained. The complete texts of these articles were carefully read, and a subset of 4 articles that were pertinent to the research question were selected. Subsequently, in October 2024, a supplementary search was conducted using Google Scholar, PubMed, and Scopus, which resulted in the identification and inclusion of three additional articles that were directly relevant to the topic of interest. To enhance the clarity and coherence of our arguments, a total of nine additional references were incorporated throughout the writing process.

Oral candidiasis

Oral candidiasis, an opportunistic infection occurring in the oral cavity, is a condition that requires considerable attention due to its impact on oral health. This infection primarily affects the elderly, particularly those who wear dentures, underscoring the vital link between proper oral hygiene and the prevention of such infections (4). Consistent and thorough oral care can often significantly reduce the risk of developing this condition. Unfortunately, oral candidiasis is frequently underdiagnosed in this age group, which may stem from insufficient awareness among healthcare professionals and caregivers regarding its symptoms and potential complications. Additionally, this condition is commonly found in individuals with weakened immune systems, serving as a possible indicator of more extensive

systemic health problems, such as diabetes mellitus, thereby highlighting the necessity for early detection and timely intervention (15, 16). The most significant pathogenic species implicated in oral candidiasis include *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*, each of which possesses unique virulence factors contributing to the infection's persistence and severity.

Given the multifaceted nature of this condition, healthcare professionals need to remain vigilant and proactive in diagnosing and managing oral candidiasis, particularly among at-risk populations. In conclusion, a comprehensive understanding of oral candidiasis, its risk factors, and its underlying causes is vital for improving patient outcomes and promoting better oral health among vulnerable groups, thereby underscoring the importance of ongoing research and education in this field (15, 17). Fungi, including various species of Candida, are characterized as eukaryotic organisms that do not perform photosynthesis and possess a cell wall situated outside the plasma membrane. The nuclear membrane features a nuclear pore complex. The plasma membrane is rich in steroids, particularly ergosterol. Generally, the cultural traits of the diverse Candida species exhibit similarities both macroscopically and microscopically.

These organisms can metabolize glucose through both anaerobic and aerobic pathways. Pseudohyphae are particularly well-suited to thrive at elevated temperatures, such as 37°C, which corresponds to the conditions found in their potential hosts. Their growth is temperature-dependent, and they can be isolated from both animal hosts and natural environments (15, 17). Various studies have demonstrated a link between specific pathogenic factors and candida infections. Key elements of the fungal cell wall, such as mannose, C3d receptors, mannoprotein, and saccharins, play a vital role in the adhesion of candida to epithelial cell surfaces, which is an essential step in the initiation of infection. Additionally, during the early stages of infection, the level of hydrophobicity and the ability to bind to host fibronectin have been identified as important factors (18, 19). Additional elements involved include the development of the germ tube, the existence of mycelia, the ability of endotoxins to remain inside epithelial cells, the production of tumor necrosis factor, and proteinases. It has also been suggested that some strains of *Candida albicans* are capable of phenotypic flipping, which is the capacity to transition between distinct morphologic phenotypes (16). Oral candidiasis typically arises as a consequence of immune suppression, which may manifest at a local or systemic level (20). Risk factors associated with the pathological colonization of Candida encompass a range of variables, including malnourishment, extremes of age (both young children and the elderly), metabolic disorders, conditions that compromise the immune system, concurrent viral or bacterial infections, exposure to radiation therapy, undergoing organ transplantation, prolonged use of steroids, administration of antibiotics, and decreased salivary gland function.

The risk of oral candidiasis might be increased by impaired salivary gland function. Saliva secretion dilutes substances and eliminates microorganisms from the mucosa (5, 16). Histidine-rich polypeptides, lactoferrin, sialoperoxidase, lysozyme, and particular anticandida antibodies are examples of antimicrobial proteins found in saliva that interact with the oral mucosa to stop the spread of candida. It has been demonstrated that medications such as inhaled steroids raise the incidence of oral candidiasis by presumably inhibiting phagocytosis and cellular immunity (16). Up to 65% of older individuals who wear complete top dentures are at risk of developing a candida infection due to their dentures. The microenvironment created by wearing dentures is anaerobic, low in pH, and favorable to the growth of candida. This might be the result of poorly fitted dentures, increased Candida spp. adhesion to acrylic decreased saliva flow beneath the surfaces of the denture fittings, or inadequate oral hygiene. The most prevalent fungal infection in humans, particularly in early and later life, is oral candidiasis (21, 22).

Research indicates that asymptomatic individuals in the general population exhibit carriage rates ranging from 20% to 75%. Specifically, 45% of newborns, 45% to 65% of healthy children, 30% to 45% of healthy adults, 50% to 65% of individuals with removable dentures, 65% to 88% of patients in both acute and long-term care settings, 90% of patients undergoing chemotherapy for acute leukemia, and between 13% and 95% of HIV-positive patients have been identified as having isolated Candida albicans infections in their oral cavities (23, 24). *Candida albicans* is a highly adaptable, polymorphic yeast-like fungus capable of significant morphological changes, including yeast, pseudohyphal, and hyphal forms, depending on

environmental conditions (25). It also engages in complex biofilm formation, where these forms are surrounded by an extracellular matrix primarily made of polysaccharides such as β-1,3 glucan, β-1,6 glucan, and α-1,2-branched α-1,6 mannan, which support the biofilm's structure and function. *C. albicans* can colonize and thrive on various surfaces, including both abiotic and biotic materials, such as medical devices and human mucosal surfaces. Biofilm formation begins with the adhesion of fungal cells to a surface, followed by their proliferation (26, 27). The fundamental mechanics underlying the initial contact between *C. albicans* cells and a surface are predominantly dictated by a complex interplay of physical and chemical interactions that govern adhesion dynamics. Moreover, the properties of the surface, including factors such as wettability, surface energy, roughness, and intricate topographical features, play a critical role in determining the degree of attachment of *C. albicans* cells (Figure 1) (28). Upon successful attachment to the surface, these cells are capable of undergoing rapid proliferation, thereby leading to the formation of a robust biofilm, which subsequently facilitates the dispersal of planktonic cells and promotes the establishment of new loci of infection. Over time, the cells that develop from these infection hotspots may potentially disseminate directly into the bloodstream, thereby gaining access to various vital organs, which include the eyes, heart valves, spleen, kidneys, and liver (29).

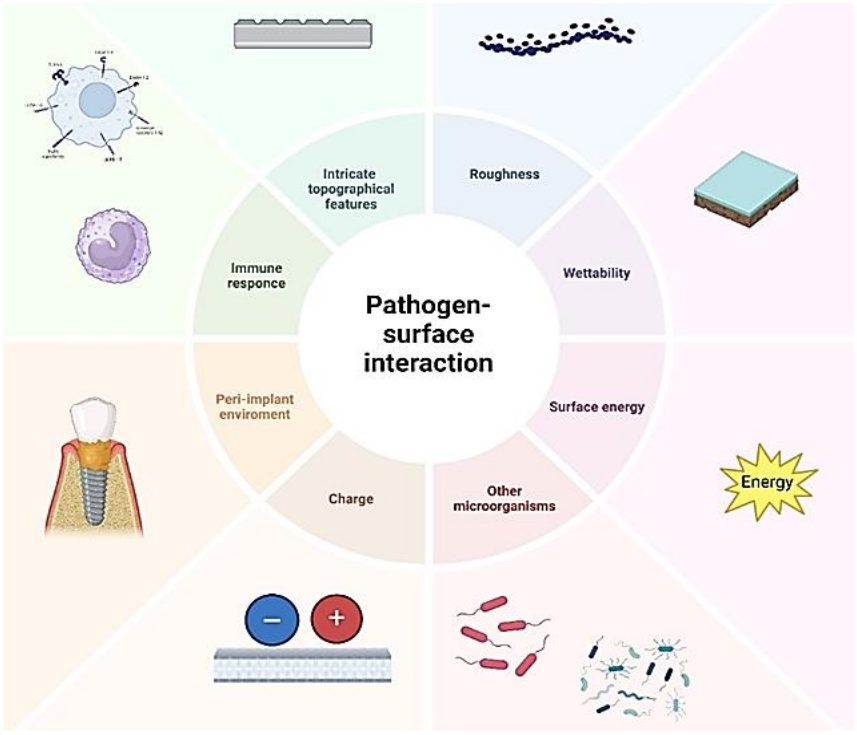

Figure 1. The properties of the surface and factors that interacted with the surface and effect on implant inflammation. The different criteria that interact with surface interaction and pathogens include, immune responses, pathogens, and improper peri-implant environment due to severe inflammation that can lead to the implant not integrating properly with the bone, which may result in the implant becoming loose or failing altogether. The type of material used for the implant (like titanium or ceramic) which are more biocompatible, can affect how well it integrates with the body and causes a less adverse reaction. The special coatings of implants beside surface properties of implants can help reduce inflammation or promote healing.

Fungal biofilms

In recent years, there has been a notable increase in the incidence of fungal infections, which has raised considerable concern in the medical community and among healthcare professionals. These mycotic diseases are responsible for contributing to over one million human fatalities annually, thereby constituting a significant and pressing health crisis on a global scale. In the current healthcare landscape,these opportunistic fungal infections predominantly target immunosuppressed or immune compromised individuals, particularly those receiving treatment in intensive care units where they are at heightened risk. The spectrum of these mycotic infections ranges from relatively

benign and non-life-threatening mucocutaneous conditions to severe invasive infections that can affect virtually any organ system within the body (30). Often, these types of fungal infections occur concurrently with other fungal or bacterial infections that can be either mild or life-threatening, and they are frequently associated with pathogenic species such as Aspergillus, various species of Candida, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, as well as *Cryptococcus neoformans* (31, 32).

Among the numerous Candida species that have been documented and thoroughly investigated, *Candida albicans* stand out as the most commonly identified and encountered fungal pathogen within the human population. Systemic candidiasis, which is instigated by the presence of *C. albicans*, is recognized as a leading cause of mortality in patients suffering from nosocomial infections and severely debilitating opportunistic fungal infections, closely followed in prevalence by *Candida glabrata*. Additionally, *Candida tropicalis* is frequently implicated in urinary tract infections (UTI), while *Candida parapsilosis* is often found in colonizing the skin of healthy individuals and is recognized as a primary causative agent in catheter-related infections (32).Moreover, it is important to note that all species within the Candida genus exhibit distinct differences in their capacity for biofilm formation, the structural characteristics of the biofilms they produce, alterations in the morphology of the extracellular matrix (ECM), and their varying abilities to resist antifungal drug treatments (27).

Fungal biofilms represent a sophisticated and intricate assembly of hyphal cells, which intricately associate not only with abiotic surfaces but also with various animal tissues, thereby resulting in a multifaceted interrelationship that is critical to their ecological and pathological roles. These biofilms are recognized as significant virulence determinants and have been closely correlated with the prevalence and severity of invasive fungal infections, as highlighted in the comprehensive study conducted by Borghi et al. in the year 2015 (33). The sessile nature of these microorganisms becomes particularly evident when they adhere to either abiotic or biotic surfaces, a process that inevitably leads to the manifestation of new and distinctive phenotypic characteristics that can alter their behavior and pathogenic potential, as demonstrated previously (34). A notable example of this phenomenon occurs with implantable medical devices, which serve as particularly advantageous environments for the formation of complex biofilm associations by the opportunistic fungus *C. albicans*, thus playing a crucial role in the etiology of a considerable proportion of clinical candidiasis cases (35).The dissemination of biofilm-associated yeast cells holds profound clinical implications, given that these cells possess the capability to initiate the formation of new biofilms or to circulate extensively throughout the host cells and tissues, ultimately contributing to the emergence of disseminated invasive diseases or candidemia.

Numerous factors that facilitate the pathogenesis of the biofilm-forming organism *C. albicans* have been documented in the scientific literature, and these factors will be examined in greater detail in the subsequent section of this discourse (2). Yeast cells initially adhered and began forming germ tubes within 3 to 6 hours. Following an incubation period of 24 to 48 hours, the mature biofilms of *C. albicans* developed into a complex structure comprising yeasts, hyphae, and pseudohyphae, with extracellular polymeric substances observable on the surfaces of certain morphological types (2). Notably, the growth conditions employed by these researchers typically do not promote filamentation in planktonic environments, indicating that specific conditions or factors present within the biofilm may trigger filament formation.*C. albicans* exhibits morphogenetic conversions, allowing it to reversibly transition between yeast and filamentous forms, which are crucial for various aspects of its biology and pathogenicity. Morphogenesis is particularly significant in the development of *C. albicans* biofilms. It demonstrated that hyphal forms are vital for maintaining the structural integrity and multilayered architecture typical of mature biofilms (3). To explore the molecular pathways that regulate filamentation and their role in biofilm formation, Ramage et al.

utilized genetically defined *C. albicans* mutant strains that were incapable of filamentation under various environmental conditions and assessed their biofilm formation capabilities. Among the mutants examined, the single *Δefg1* and double *Δcph1/Δefg1* deletion mutants failed to filament and produced suboptimal biofilms characterized by a lack of three-dimensional structure, primarily consisting of sparse monolayers of elongated cells (2). The findings indicate that the Efg1 regulatory protein is crucial for the formation and

maturation of *C. albicans* biofilms on both biological and artificial surfaces (36). However, this role may stem from its filamentation defect, as strains with mutations in other genes associated with filamentation also exhibit impaired biofilm formation. Nonetheless, it remains possible that dimorphism is not an absolute requirement for biofilm formation, given that substantial yeast-only biofilms have been documented, although it may be necessary for the development of a spatially organized structure (31). It is still possible that dimorphism itself is not an essential requirement for biofilm formation, as significant yeast-only biofilms have been documented. However, it may be crucial for the establishment of the spatially organized structures observed in mature, well-structured biofilms.

The extracellular matrix (ECM) serves as a critically essential characteristic of biofilms, as it provides a protective barrier for the adherent cells, safeguarding them from the host's immune responses and the detrimental effects of antifungal agents through the establishment of complex and extensive matrix structure (37). In several pioneering studies, it has been demonstrated that the matrices of biofilms formed by various species of Candida exhibit an increase when exposed to highly dynamic flow environments, indicating that the quantity of extracellular matrix is heavily influenced by both the specific strain and the particular species of Candida involved. Furthermore, the chemical composition of the extracellular matrix associated with *C. albicans* reveals that it is comprised of approximately 55% glycoproteins, while carbohydrates contribute only 25% to the overall matrix composition (35).

The carbohydrate components predominantly consist of polysaccharides such as α-mannan and β-1, 6-glucan, with β-1, 3-glucans contributing a relatively minor proportion. The ECM is also composed of approximately 15% lipids and a mere 5% nucleic acids. Notably, β-1, 3-glucan is instrumental in conferring resilience to azole antifungal agents through specific binding interactions (38). Additionally, it has been observed that the thickness of the biofilm is approximately double that of planktonic cells. A comparative analysis of the chemical compositions of planktonic and biofilm cells has revealed distinct differences in both carbohydrate and β-1, 3-glucan compositions (39, 40). The presence of extracellular DNA within the extracellular matrix is a significant factor contributing to the overall structural stability of the *C. albicans* biofilm. It is found in both bacterial and fungal biofilms; consequently, when these biofilm-forming microorganisms undergo treatment with DNAase enzymes in conjunction with their respective antifungal agents, a marked reduction in the biofilm matrix is typically observed (39, 40).

A variety of genetic factors, including Bcr1, which is a transcription factor essential for the adherence of fungal cells to abiotic surfaces, as well as Rlmp, Brg1, Efg1, Ndt80, Rob1, Tec1, Fsk1p, Smi1p, Gcr1, and Mnn4, are currently the subject of intensive research. All of these genetic factors work synergistically and interact with various genes to regulate and orchestrate biofilm formation, thereby providing valuable new insights into the mechanisms underlying biofilm development (41).

Another significant mechanism associated with the extracellular properties of the *C. albicans* matrix pertains to the phenomenon of quorum sensing, which plays a crucial role in the growth and maintenance of biofilms (42). Quorum sensing is characterized by a density-dependent cell-to-cell communication process, wherein autoinducers, or signaling molecules, are released in response to an increase in cell density, leading to the enhancement or repression of the activation of specific genes or factors (43). This density-dependent communication mechanism has profound implications for various aspects of microbial behavior, including pathogenesis, morphological characteristics, and cellular competence, and importantly, it also contributes to the intricate process of biofilm formation.

Historically, quorum sensing was regarded as a characteristic feature exclusive to certain bacterial systems; however, the recent identification of farnesol, a quorum-sensing molecule known to inhibit biofilm formation in *C. albicans*, has significantly broadened the understanding of quorum sensing mechanisms (42, 44). Moreover, genetic regulation of virulent genes in pathogenic microorganisms mediated by quorum sensing has revealed an indirect correlation with the emergence of multi-drug resistant pathogens. Consequently, this situation underscores the urgent need for the development of alternative strategies aimed at targeting quorum-sensing mechanisms to effectively restrain biofilm formation and combat the associated clinical challenges (42). The immune system is fundamentally integral to the processes involving the detection and subsequent eradication of

the opportunistic pathogen known as *C. albicans*, which poses a significant threat to host organisms. Specifically, the innate immune system serves as the foremost line of defense against such pathogens, adeptly recognizing pathogen-associated molecular patterns unique to the pathogenic strain of *C. albicans*. This recognition triggers a cascade of signaling pathways within the host organism, ultimately leading to the effective extermination of the *C. albicans* cells that are present and proliferating (20, 45, 46). Recent empirical research has revealed that there are at least ten unique surface receptors involved in this intricate recognition process.

Among these are Toll-like receptors, including TLR4, TLR2, and TLR9, as well as the internal receptor NLR Family Pyrin Domain Containing 3 (NLRP3). Furthermore, C-type lectin receptors such as Dectin-1, Dectin-2, Dendritic Cell-Specific Intercellular Adhesion Molecule-3-Grabbing Non-Integrin (DCSIGN), Mincle, and Mannose-Binding Lectin also play significant roles in this complex system (47, 48). Generally, these receptors can identify and bind to specific sugar structures, such as β-1, 3-glucans, and various mannose derivatives, which are prevalent on the surface of *C. albicans*.

The binding interactions that occur as a result of this recognition play a pivotal role in the activation of the cytokine complement system, which in turn facilitates the phagocytosis of the fungal cells. Furthermore, the internal uptake of these fungal cells by antigen-presenting cells (APCs) significantly accelerates the activation of internal receptors; this leads to a consequential activation of either TLR9 or the NLRP3 inflammasome.

This non-specific immune response, better known as the innate response, is of immense significance in thwarting potential *C. albicans* infections. Moreover, the adaptive immune response contributes to this defense mechanism by producing specific antibodies aimed at targeting certain extracellular proteins, thereby obstructing the growth and proliferation of *C. albicans* (47, 49). *C. albicans* has developed a range of strategies to effectively evade the strong immune responses of the host. The mature biofilms formed by *C. albicans* can avoid immune detection due to an outer layer primarily made up of hyphal cells, which obscure the β-glucans in the biofilm structure. As a result, these hyphal cells can escape neutrophil-mediated destruction either by invasive growth that allows them to penetrate epithelial layers or by physically infiltrating and residing within host cells (49). The variations in gene expression between planktonic and biofilm cells are closely linked to the mechanisms of immune evasion. Several proteins that are highly expressed inhibit the activation of the host complement system.

Key examples include the Zinc-binding cell surface protein Pra1, the cell surface glycerol-3-phosphate dehydrogenase Gpd2, and a range of secretory proteins from the aspartyl protease family (Sap). Furthermore, Msb2, a well-studied protein that senses cell wall damage and is expressed at higher levels in biofilms, plays a vital role in secreting factors that inhibit the action of antimicrobial peptides, thereby preventing the activation of the complement system (25). The influence of *Candida albicans* on biofilm development on implant surfaces is considerable, as it facilitates microbial colonization and increases resistance to antifungal therapies. Research shows that *C. albicans* not only boosts the biomass of biofilms but also supports the survival of different periodontal bacteria on dental implants.

Additionally, the surface properties of implants, including roughness and wettability, are essential factors in the adhesion and proliferation of *C. albicans* biofilms. Bravo et al., 2024 study revealed that *Candida albicans* significantly exacerbated biofilm development on dental implant surfaces, increasing bacterial biomass and cell viability. After 48 and 72 hours, there was a notable rise in counts and viability of periodontal bacteria, including *Fusobacterium nucleatum* and *Porphyromonas gingivalis* (50). Additionally, a recently published article manifested that *Candida albicans* significantly impacts biofilm formation on implant surfaces, as it readily attaches and forms highly antifungal-resistant biofilms. Modifying surface properties like wettability and topography can reduce initial attachment, thereby decreasing infection severity and the need for antifungal treatments (51).

The study by Heng Z in 2023, focused on 26 clinical isolates of *Candida strains*, including *Candida albicans*, demonstrating that these strains formed biofilms on titanium surfaces. Chlorhexidine combined with azoles significantly inhibited biofilm formation, highlighting the challenge of Candida infections in orthopedic implants (52).

The impression of dental implant surface changes on biofilm formation

The timeline of dental implants extends back to 600 A.D. when the Mayans utilized shells as a means to replace lost teeth. The modern phase of dental implant development started in the 1930s with the introduction of endosteal implants constructed from Vitallium. This evolution reached a critical point in 1965 with Dr. Per-Ingvar Brånemark's launch of titanium implants, which significantly advanced both the stability and documentation of these dental solutions (50, 51).

Various material properties, including surface roughness, hydrophobicity, electrostatic interactions, material composition, matrix type, filler size, and filler arrangement, significantly influence the attachment of organisms to surfaces, leading to biofilm formation (53). Surface roughness, in particular, is well-established as a critical factor in microbial adhesion. This characteristic determines the available area for bacterial attachment and the level of protection afforded to colonizing bacteria. Research indicates that higher populations of *C. albicans* are present on rough surfaces compared to polished, smooth ones.

Consequently, it is theoretically advisable for dental materials to be polished in situ to achieve the smoothest possible surface (53, 54). Currently, dental implants are frequently chosen for oral prosthetic procedures. Microbial adhesion on the surfaces of these implants or their prosthetic components can lead to significant clinical issues, including mucositis, peri-implantitis, and stomatitis. Additionally, *C. albicans* can readily colonize dental materials, resulting in severe infections. There exists a direct correlation between the level of adhesion, which leads to colony formation, and the onset of related diseases. Success criteria for dental implants encompass several factors, including immobility, the absence of radiolucency, minimal bone loss, and no complications.

Nevertheless, 1-2% of implants may fail due to insufficient osseointegration, while approximately 5% may experience secondary failure due to peri-implantitis (55). The repercussions of implant failure can be significant, resulting in health complications, increased financial burdens, and challenges in achieving optimal function and aesthetics. Replacing failed implants often leads to lower survival rates, particularly when bone conditions are compromised. Osseointegration refers to the direct bond between living bone and the implant surface, involving both primary stability at the time of placement and secondary stability as healing occurs. The characteristics of the implant, especially its surface, play a vital role in this process (56). The implant surface is critical for osseointegration and biofilm development. Textured surfaces can improve bone contact and stimulate cellular responses that enhance osseointegration.

However, the interplay between biofilm formation and bone growth is crucial, as biofilms can contribute to complications such as peri-implantitis. Achieving a balance between antimicrobial properties and osteoconductivity is vital for the successful implementation of dental implants (50). Surface roughness plays a crucial role in influencing osseointegration and biofilm development. For optimal bone fixation, a roughness range of 1-1.5 µm is essential, whereas maintaining a threshold of 0.2 µm is vital to minimize bacterial retention.

The results indicate that micro-scale alterations to titanium implants are most beneficial for osseointegration, while nano-scale changes are more effective in reducing bacterial adhesion. This suggests that varying approaches may be necessary based on the specific objectives. The research underscores that chemical modifications, especially those enhancing hydrophilicity, can facilitate osseointegration and concurrently decrease bacterial adhesion. This dual advantage is critical for enhancing the performance of implants (6). Additionally,growth factor coatings improve osseointegration; while antibacterial coatings combat bacterial colonization effectively. This implies that a multifaceted strategy may produce the most favorable outcomes.

While alternative materials such as zirconia and PEEK have been investigated, the study indicates that clear conclusions regarding their benefits compared to titanium are still lacking. This highlights the necessity for further exploration in this domain (57, 58). Inadequate osseointegration and persistent inflammation are two key contributors to the development of dental peri-implantitis. Immune cell infiltration affects the biocompatibility and function of dental implants, potentially causing failure. Initial peri-implant tissue damage triggers inflammation mediated by innate immune cells like macrophages, dendritic, mast, and neutrophils (12). Biofilm formation on implant surfaces also induces immune responses and inflammation (Figure 2) (59).

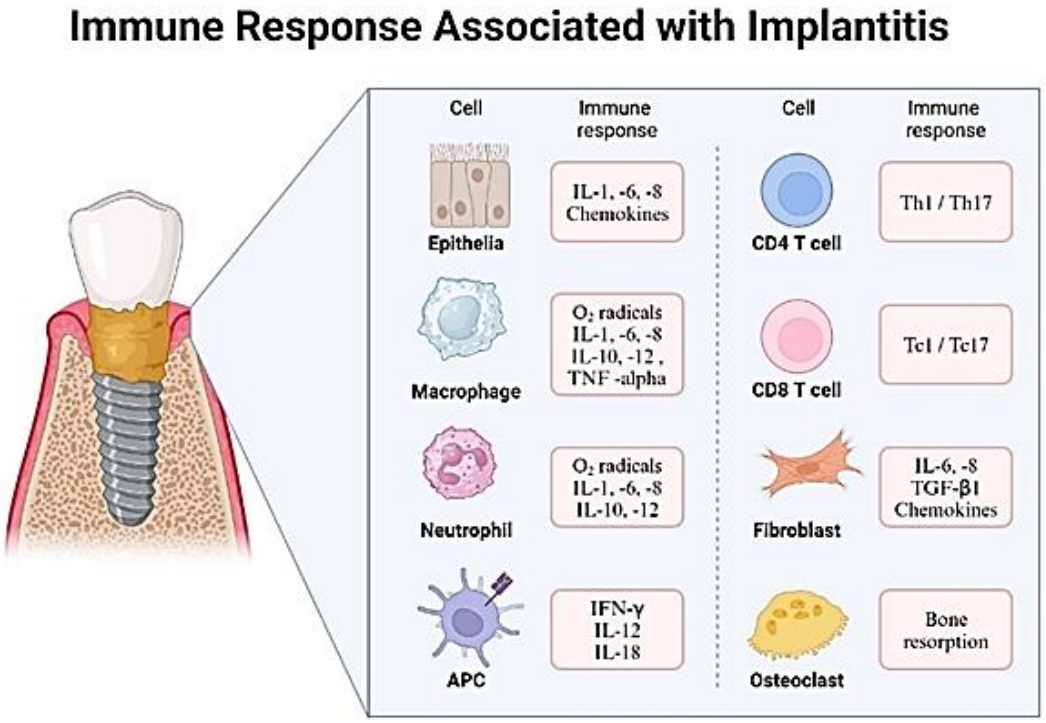

Figure 2. Immune responses associated with implant inflammation due to pathogens invasion. When the immune system detects the presence of these pathogens, it triggers an inflammatory response. This response includes neutrophils, macrophages, APC, and lymphocytes that release IL-12, 18, 1, 6,8,10, IFN, and TNF-alpha. They can promote inflammation and attract more immune cells to the site of infection. While the immune response is essential for fighting off infections, it can also lead to tissue damage if it is too strong or prolonged. This can result in bone loss, pain, and discomfort due to swelling, redness, and pain in the area around the implant.

Pro-inflammatory

Interleukin-1 (IL-1) isoforms, particularly IL-1α and IL-1β, are linked to bone resorption and osteoclast activation, playing a significant role in peri-implantitis. Elevated levels of IL-1β in peri-implantitis lesions correlate with gingival inflammation, making it a potential early diagnostic marker for peri-implant mucositis. Other proinflammatory cytokines, such as TNF-α and IL-17, are also implicated in the inflammatory response associated with implant failure, highlighting their potential as biochemical markers in Peri-Implant Crevicular Fluid (PICF) (60).

Anti-Inflammatory

IL-10 serves as a crucial immune modulator that suppresses proinflammatory cytokine production, although its levels can vary in peri-implantitis cases. TGF-β1 is another anti-inflammatory factor involved in wound healing and immune regulation, with conflicting reports on its expression in peri-implantitis. The roles of anti-inflammatory cytokines like IL-10 and TGF-β1 in dental implant rejection remain unclear, suggesting a need for further investigation in this area (61, 62).Fungal biofilms represent some of the most challenging infections to manage due to their significant resistance to antifungal treatments and their strategies for evading the immune system. The prevalence of fungal biofilm infections is expected to increase, particularly with the rising number of patients with implanted medical devices and those with compromised immune systems. There is an urgent need for anti-biofilm therapies. Gaining insights into the dynamics of biofilm formation, matrix production, and the ways these processes confer resistance to various aspects of the innate immune system could pave the way for the development of biofilm-targeted antifungal treatments.

The adoption of a biofilm lifestyle during fungal infections is increasingly acknowledged as a strategy to evade host immune responses and create a protective environment. Within this setting, the extracellular matrix can obscure the fungal cell wall from detection by host cells, thereby modulating the immune reaction (59). Additionally, the extracellular matrix offers

defense against antimicrobial agents, including defensins, oxidative stress, and neutrophil extracellular traps (NETs). Moreover, the formation of biofilms results in a clustered community that may resist phagocytic engulfment. While the impact of biofilm formation on immune responses is well established, research is just beginning to explore the various mechanisms that contribute to this modulation of host defenses. Given that biofilms are heterogeneous, with differences in structure and composition depending on their environmental context, the mechanisms that hinder immunity are likely to differ among clinical biofilms. Consequently, it is essential to incorporate conditions that closely replicate the host environment and utilize animal models of biofilm infection in future research. Although recent investigations have highlighted the effects of biofilm formation on the innate immune response, there remains a limited understanding of how these structures may influence adaptive immunity (63).

Other Factors

Matrix metalloproteinases (MMPs), particularly MMP-8, are significant in the inflammatory process of peri-implantitis and are associated with early signs of implant failure. The balance between RANKL and OPG is critical for osteoclast regulation, with increased RANKL and decreased OPG levels observed in peri-implantitis compared to healthy sites. Osteopontin (OPN) may influence IL-1β production and apoptosis in peri-implantitis, indicating its role as an immune modulator and a potential prognostic marker for dental implant outcomes (64).

Adherence of fungal cells to available biomaterials in the oral cavity

Moreover, the process of adherence of fungal cells to available biomaterials, coupled with their association with bloodstream infections, may be attributed to the hematogenous spread of the pathogen throughout the host, underscoring the clinical significance of these interactions. Medical devices, due to their unique structural properties and chemical characteristics, ranging from hydrophobicity to varying degrees of surface roughness, create an ideal niche for yeast cells to thrive and proliferate (35). These devices are often enveloped by various body fluids, including but not limited to urine, blood, saliva, and synovial fluid, which condition their surfaces with a glycoproteinaceous film that alters the chemical properties of the original material, as articulated by Gristina et al. in 1988 and further supported by Subbiahdoss et al. in 2010 (65, 66). This acclimatizing film possesses the potential to confer entirely different chemical properties compared to those of the underlying surface. The maturation of the biphasic structure of *C. albicans* is significantly influenced by both non-specific factors, such as cell surface hydrophobicity and electrostatic forces, as well as specific adhesins present on the fungal surface that recognize ligands within the conditioning films, including serum proteins like fibrinogen and fibronectin, alongside salivary components (53). Additionally, *C. albicans* cells exhibit the capability to co-aggregate and interact with pre-existing bacterial cells or colonies that are already established on these medical devices.

Nevertheless, the initial focal attachment of the fungal cell to a suitable substratum is invariably coupled with the processes of multiplication and propagation of these cells, which subsequently leads to the elaborate development of biofilms (67). Research has demonstrated that the development of biofilms adheres to a series of sequential steps that typically unfold over some time of 24 to 48 hours, as detailed in the previous studies. The initial stage of this process involves a single yeast cell achieving adherence to the substratum, thereby establishing a foundational layer for subsequent yeast cell accumulation, which is referred to as the adherence step (68). Following this foundational phase is characterized by a phase of cell proliferation, during which the cells extend outward and continue to develop into the filamentous structures known as hyphal cells that penetrate through the surface, marking what is termed the initiation step.

The subsequent assembly of hyphae signals the commencement of biofilm formation, a process that is accompanied by the gradual accretion of an extracellular matrix as the biofilm matures, and a phenomenon referred to as the maturation step. Finally, in the last phase of this intricate process, non-adhering yeast cells detach themselves from the established biofilm, allowing them to disperse into the surrounding environment in search of new and favorable sites for attachment, which is described as the dispersal step (1). Biomaterial-associated infections (BAI) represent a primary challenge in the longevity of biomaterial implants. The introduction of microbial contaminants during surgical procedures (peri-operative contamination)

or hospital stays is a significant factor in the development of BAI. The microorganisms involved in BAI often exhibit resistance due to their growth in biofilms. The prevalent use of indwelling catheters, especially central venous and hemodialysis types, has notably increased the occurrence of fungal bloodstream infections, particularly candidiasis (65, 64, 68). Historically, to mitigate the risk of nosocomial infections stemming from central line-associated bloodstream infections (CLABSIs), the standard practice involved the removal of the infected devices and the administration of systemic antimicrobial treatments to eliminate these pathogens (65).

Biomedical devices made from various biomaterials are frequently exploited by pathogenic fungi such as *C. albicans*, facilitating their adhesion, colonization, and subsequent biofilm development. Consequently, there is a growing interest in the creation and enhancement of innovative biomaterials that deter microbial (both fungal and bacterial) adhesion and colonization on the surfaces of implanted devices (65). Some research suggests that modifying the surface chemistry of biomaterials may effectively prevent or diminish biofilm formation. This can be accomplished by incorporating surface-modifying end groups (SMEs) or by adjusting the chemical makeup of the substrates. For instance, the addition of SME Polyether urethane to the biomaterial Elasthane 80A significantly reduced the ability of *C. albicans* to form biofilms (69).Based on a previous study, the biofilm formation of *Candida albicans* on various polymeric surfaces, including polypropylene (PP), polystyrene (PS), polyvinyl chloride (PVC), and silicone rubber (SR) was evaluated. The results indicated that the highest levels of biofilm formation were observed on PS, PP, and SR, with percentages of 64.19%, 50.31%, and 45.09%, respectively, when compared to PVC after 48 hours, as measured by the XTT tetrazolium reduction assay.

The production of exopolysaccharides (EPS) during biofilm formation was quantified using the acetone precipitation method, yielding values of 11.45 µg/cm² for PVC, 9.41 µg/cm² for PS, 8.65 µg/cm² for PP, and 6.95 µg/cm² for SR. Atomic force microscopy and goniometric analysis revealed that PVC exhibited the highest roughness (134 nm) and hydrophobicity (97°). Confocal laser scanning microscopy (CLSM) further demonstrated that PVC had the greatest biofilm thickness, measuring 117.5 µm, as determined through z-sectioning. Scanning electron microscopy (SEM) corroborated these findings regarding biofilm growth on the various biomaterials. The results suggest that PVC is particularly prone to *C. albicans* biofilm formation, with surface properties such as roughness and hydrophobicity facilitating the adhesion and development of the biofilm (70). Previous investigations focused on comparing the adhesion susceptibility of six different implant materials to *C. albicans*. The attachment of organisms to surfaces, which leads to biofilm development, is influenced by a range of material characteristics, including surface roughness, hydrophobicity, electrostatic forces, material composition, matrix type, filler size, and configuration. Among these, surface roughness is particularly well-established as a key factor in microbial adhesion. This property impacts the extent of the surface area available for bacterial attachment and the degree of protection for colonizing bacteria. Studies have shown that rough surfaces tend to support greater populations of *C. albicans* than their polished counterparts.

Therefore, it is theoretically recommended that dental materials be polished in situ to create the smoothest surface possible. The materials were evaluated from various angles and regions; however, the study did not explore the correlation between surface roughness and candidal adhesion, which restricts the ability to link the results to specific surface characteristics (71). The results of in vitro investigations suggest a strong correlation between the degree of surface roughness and the amount of *C. albicans* that adhere. In the other site, seven frequently utilized implant and restorative materials were evaluated. The average surface roughness of all materials was restricted to a range of 0.07–0.10 µm. Measurements were taken for contact angles and salivary mucin absorption. Following an initial adhesion period of 90 minutes and a subsequent 2-day biofilm development, the quantities of *C. albicans* were quantified by counting colony-forming units, while morphological characteristics were examined using scanning electron microscopy (SEM). The impact of saliva coating and the effects of material surface properties on initial adhesion, biofilm formation, and its removability were analyzed through univariate two-way analysis of variance and multiple linear regression analysis. The surface contact angle of the materials, which serves as an indicator of hydrophobicity, was positively correlated with both initial adhesion and biofilm formation of *C. albicans*. Conversely, a negative

correlation was observed between mucin absorption and the removability of Candida biofilm, suggesting that mucin significantly contributes to biofilm formation and its structural integrity. SEM analysis indicated a lower presence of Candida cells on saliva-coated titanium compared to saliva-coated hydroxyapatite or acrylic resin (72). Materials exhibiting varying hydrophobic properties and compositions demonstrated distinct patterns in salivary mucin absorption, initial adhesion, and biofilm formation. Hydrophobic materials facilitated greater initial adhesion, leading to more pronounced biofilm development (73). Mucin plays a critical role in the immobilization of Candida and the progression of biofilm formation on these materials. The hydrophilic characteristics and composition of materials, along with salivary proteins—particularly mucin—significantly influence the process of Candida biofilm formation, as well as the quantity and rigidity of the resulting biofilm. The findings presented may serve as a valuable reference for the selection of materials in implant overdenture treatments from a microbiological perspective (74).

The formation of biofilms on the surface of implants is closely tied to the ability to cause infections, highlighting its significance as a virulence factor in candidiasis. This biofilm lifestyle not only leads to resistance against antifungal agents but also provides a shield against host immune defenses, which has serious clinical implications. Molecular investigations into biofilm development are beginning to reveal the underlying mechanisms that drive this transition, including quorum sensing, which may open up new avenues for treatment future research should focus on in vivo biofilms, the dynamics of mixed bacterial-fungal biofilms, the biofilm-forming potential of other Candida species, and the investigation of new implant materials and strategies to prevent biofilm formation. *Candida albicans* biofilms typically have a bi-layered structure, with a lower layer of yeast firmly attached to the surface and an upper layer comprised of hyphae. The overall architecture varies depending on the energy source and growth conditions. Biofilms develop similarly in vivo and in vitro, but in vivo, models mature faster and form thicker walls.

Treating these biofilms is challenging due to their significant resistance to antifungal therapies, largely attributed to their glucan-rich extracellular matrix and impermeable structures. Recent studies have shown a strong link between *C. albicans* resistance and candidiasis recurrence, particularly involving a subset of cells called persister cells. These metabolically inactive cells within biofilms exhibit remarkable resilience to antifungal treatments and remain unaffected by attempts from medications and the host's immune response to eliminate *C. albicans* biofilms. Alarmingly, research indicates that once antifungal treatment ceases, these resilient cells aid in repopulating the biofilms (74-76).

Discussion

Candida albicans is a significant factor in biofilm-associated infections, especially within oral environments. Its proficiency in adhering to diverse surfaces, such as dental implants, plays a pivotal role in the formation of pathogenic biofilms. The investigation underscores that biofilms are intricate structures that afford protection to microorganisms, thereby rendering them resistant to standard antimicrobial interventions. This intricacy complicates the management of infections linked to dental implants. The research indicates that the nature of implant surfaces profoundly influences biofilm formation.

Surfaces with rough textures are more likely to support greater biofilm accumulation compared to their smoother counterparts, which can affect the overall efficacy of the implant. There exists an urgent necessity for the advancement of biomaterials with modified surfaces capable of mitigating biofilm development. The proposal of antimicrobial coatings that specifically target fungal pathogens is presented as a promising strategy to enhance the durability and efficacy of dental implants. The results highlight the significance of continuous research aimed at elucidating the interactions between *C. albicans* and implant surfaces. This understanding is critical for formulating effective methods to avert biofilm-related infections and enhance patient outcomes within dental practices. In conclusion, the research offers significant insights into the involvement of *C. albicans* in biofilm development on implants, emphasizing the necessity for innovative solutions to address these infections.

Study limitations

The present review examines the effects of *Candida albicans* on biofilm formation, particularly concerning dental implants. However, it may not sufficiently consider variations in biofilm behavior among different populations or demographics, such as age, health conditions, or

specific risk factors linked to oral candidiasis. The insights regarding the interactions between C. albicans and various implant surfaces may not be applicable across all dental implants or biomaterials. Differences in material characteristics, surface modifications, and individual patient factors could result in varied outcomes that are not thoroughly addressed in the study.

Future directions and research opportunities

There is a need for more in vivo studies to understand the dynamics of biofilm formation in real biological environments. This research could provide insights into how *C. albicans* interact with host tissues and other microorganisms in a natural setting. Future investigations should focus on the dynamics of mixed bacterial-fungal biofilms. Understanding how *C. albicans* interact with other microbial species could reveal new strategies for managing biofilm-related infections. Research should also explore the biofilm-forming potential of other Candida species. This could help us understand the broader implications of fungal infections and their treatment. Investigating new materials and surface modifications for dental implants is crucial. The study suggests that surfaces promoting osteoblast growth and reducing biofilm formation could significantly enhance the success of implants. Further molecular investigations into the mechanisms driving biofilm development, such as quorum sensing, could open new avenues for treatment. Understanding these processes may lead to innovative therapeutic strategies to disrupt biofilm formation. The development of antimicrobial coatings that can effectively kill fungi on contact is a promising area for future research. Such coatings could significantly reduce the incidence of biofilm-related infections in dental implants. Continued research into how surface properties (e.g., wettability, roughness) influence the attachment and growth of *C. albicans* is essential. This knowledge can guide the design of more effective dental materials. The summary of biofilm culture and evaluation for drug development is indicated in Figure 3.

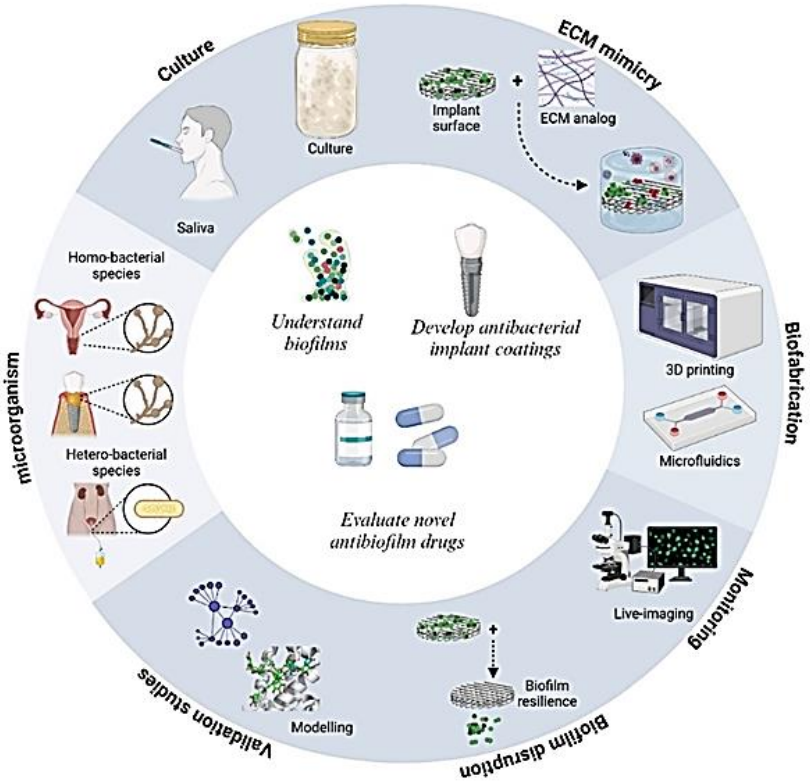

Figure 3; The figure summarizes the key aspects of biofilm research, including the types of pathogens involved, methods for evaluating and isolating them, and the future directions for improving health care. The novel approach is vital for developing strategies to combat infections caused by biofilms, ultimately leading to better health for individuals at risk. The future directions in biofilm research focus on finding better ways to prevent and treat infections caused by biofilms. This includes developing new materials for medical devices that resist biofilm formation or creating treatments that can effectively target and destroy biofilms besides looking into using antimicrobial coatings that kill pathogens on contact, rather than slowly releasing medication over time.

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