HHS Public Access

Author manuscript

Environ Microbiol Rep. Author manuscript; available in PMC 2023 April 01.

Published in final edited form as:

Environ Microbiol Rep. 2022 April ; 14(2): 183–196. doi:10.1111/1758-2229.13053.

In it together: Candida-bacterial oral biofilms and therapeutic strategies

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Summary

Under natural environmental settings or in the human body, the majority of microorganisms exist in complex polymicrobial biofilms adhered to abiotic and biotic surfaces. These microorganisms exhibit symbiotic, mutualistic, synergistic, or antagonistic relationships with other species during biofilm colonization and development. These polymicrobial interactions are heterogeneous, complex, and hard to control, thereby often yielding worse outcomes than monospecies infections.

Concerning fungi, *Candida* spp., in particular, *Candida albicans* is often detected with various bacterial species in oral biofilms. These Candida-bacterial interactions may induce the transition of *C. albicans* from commensal to pathobiont or dysbiotic organism. Consequently, Candida–bacterial interactions are largely associated with various oral diseases, including denture stomatitis, dental caries, periodontitis, peri-implantitis, endodontic infections, and oral cancer. Given the severity of oral diseases caused by cross-kingdom consortia that develop hard-to-remove and highly drug-resistant biofilms, fundamental research is warranted to strategically develop cost-effective and safe therapies to prevent and treat cross-kingdom interactions and subsequent biofilm development. While studies have shed some light, targeting fungal-involved polymicrobial biofilms has been limited. This mini-review outlines the key features of Candida-bacterial interactions and their impact on various oral diseases. In addition, current knowledge on therapeutic strategies to target Candida-bacterial polymicrobial biofilms is discussed.

Keywords

Candida albicans; bacteria; cross-kingdom biofilm; oral diseases; therapeutics

Introduction

In a wide variety of environments from natural settings to the human body, the majority of microorganisms exist in complex polymicrobial biofilms adhered to abiotic and biotic surfaces. During biofilm colonization and development, microbes exhibit symbiotic, mutualistic, synergistic, or antagonistic relationships with other species. Those

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polymicrobial biofilms are often detrimental, causing food spoilage, industrial pipe fouling and corrosion, as well as human infectious diseases. Specifically, polymicrobial biofilms can cause various infections in a wide range of the human body, from the oral cavity (Kolenbrander 2000, Schaudinn et al. 2009) to lung (Stressmann et al. 2012, Zhao et al. 2012, Filkins et al. 2015) to urinary tract (Ronald 2002, Kline et al. 2016) to chronic wounds (Gjødsbøl et al. 2006, Dowd et al. 2008). These polymicrobial biofilms tend to be challenging to treat and often yield worse outcomes than monospecies infections by altering the sensitivity to antimicrobial agents (Orazi et al. 2019).

The gastrointestinal tract and the oral cavity are the representative human body parts that harbor a complex and diverse multitude of microorganisms, where they serve an essential role in local and systemic health. In particular, the oral cavity is a unique ecosystem that contains 600 to 1,000 bacterial species as well as more than 100 fungal species, colonizing soft and hard tissues either permanently or transiently (Aas et al. 2005, Manson et al. 2008, Peters et al. 2012a, Brown et al. 2019). In health, commensal microbiota inhibits pathogen colonization while supplying the host with essential nutrients, maintaining a stable micro-ecosystem (Martín et al. 2013, Negrini et al. 2021). However, disruptions of such commensal microbial communities from steady-state composition may result in the imbalance of host-microbiome interaction and illness (Negrini et al. 2021). Although clinical evidence indicates that the coexistence of bacteria and fungus in the oral cavity may accelerate susceptibility to host infection, previous oral biofilm studies have largely focused on the development of bacterial biofilms (mostly monospecies), and the aspect of cross-kingdom interactions have been underexplored. However, recent mechanistic studies exhibit the role and importance of bacterial-fungal interactions during biofilm formation and development as well as their implication in oral health and disease states.

Concerning fungi, *Candida* spp. are the most commonly detected fungal species in the oral cavity (Ghannoum et al. 2010, Dupuy et al. 2014, Witherden et al. 2017, Delaney et al. 2019). Particularly, *C. albicans* is often found with various bacterial species in oral polymicrobial biofilms which may induce the transition of *C. albicans* from commensal to pathobiont or dysbiotic organism (O'Donnell et al. 2015, Janus et al. 2016, Delaney et al. 2018, Xiao et al. 2018, de Cássia Negrini et al. 2019). In this cross-kingdom interaction, the cell wall of *C. albicans*, a critical structure for maintaining the cell shape and immunogenicity (Hall et al. 2013), plays an important role as the major point of contact between the fungus and bacteria (Buurman et al. 1998, Hoyer 2001). For example, hypha-specific adhesins, ALS (agglutinin-like sequence) group of cell wall glycoproteins (e.g., Als1 and Als3), are shown to mediate the cross-kingdom interaction of *C. albicans* with various bacteria commonly found in the oral cavity, such as *Streptoccus gordonii* (Silverman et al. 2010, Bamford et al. 2015), *Streptococcus oralis* (Xu et al. 2017), *Porphyromonas gingivalis* (Sztukowska et al. 2018), *Staphylococcus aureus* (Peters et al. 2012b), and *Staphylococcus epidermidis* (Beaussart et al. 2013). These Candida–bacterial interactions have been found to be associated with various oral diseases including dental caries, denture stomatitis, periodontitis, peri-implantitis, and oral cancer. Unfortunately, drug susceptibility studies revealed that it is challenging to eradicate those Candida-bacterial polymicrobial biofilm-induced diseases due to alterations of the efficacy of antibiotics by either fungal

cells or bacteria (Jenkinson et al. 2002) and lack of targeting polymicrobial interactions (Kim et al. 2021).

This mini-review aims to present the characteristics of Candida-bacterial interactions and their impact on polymicrobial biofilm formations in the context of various oral diseases. In addition, diverse therapeutic strategies to target Candida-bacterial polymicrobial biofilms are introduced.

Candida-bacterial biofilm-associated oral diseases

Bacterial colonization and biofilm formation on tooth surfaces or oral soft tissues are modulated by the type of species that initially bind and subsequent colonizers interacting with those. Candida-bacterial cross-kingdom interactions may also participate in those processes and affect biofilm development, thus contributing to the severity of biofilm-associated oral diseases. There are numerous pieces of evidence showing that the association of *C. albicans* and various bacteria is implicated in diverse aspects of oral diseases (Figure 1), which are summarized in the following subsections.

Dental caries

Dental caries, also known as tooth decay, is a representative biofilm- and diet-dependent oral disease (Sheiham et al. 2015, Bowen et al. 2018). Among various fermentable sugars, sucrose is considered the most cariogenic (Leme et al. 2006) due to its contribution to biofilm formation and development by serving as a substrate for the production of extracellular polysaccharides (EPS) (Bowen et al. 2018). While bacteria have been traditionally considered as a major component of the etiology of dental caries (Thomas et al. 2012, Wolff et al. 2013, Simón-Soro et al. 2015), many recent studies revealed that *C. albicans* are often detected from plaque biofilms, particularly in children with severe early childhood caries (ECC) (Hajishengallis et al. 2017, Jean et al. 2018, Xiao et al. 2018, Garcia et al. 2021). Specifically, synergistic interaction between *C. albicans* and cariogenic bacterium *Streptococcus mutans* is heavily studied *in vitro* and *in vivo* in the context of dental caries (Falsetta et al. 2014, Ellepola et al. 2017, He et al. 2017, Hwang et al. 2017, Kim et al. 2017). The consensus is that EPS produced by *S. mutans* plays an important role in mediating *C. albicans-S. mutans* cross-kingdom interaction, generating a virtuous cycle whereby it enhances *C. albicans* growth and metabolic activity, in turn, accelerating *S. mutans* growth and EPS production as well. This enhanced EPS production also facilitated the surface coating of *C. albicans* with EPS, established the alliance between *C. albicans* and *S. mutans* at an early stage of biofilm development, thereby outperforming *S. gordonii* in a 3-species mixed biofilm model (Figure 2) (Wan et al. 2021). Interestingly, a more recent study showed that only *C. albicans-S. mutans* cross-kingdom biofilm matured and created an acidic microenvironment when cultured in human saliva, while *S. mutans* alone were not successful (Kim et al. 2020). In addition, a variety of other factors that involved in *C. albicans-S. mutans* interaction has been discussed. For example, one study revealed that the removal of extracellular DNA disrupted the initial stage of cross-kingdom biofilm formation (Guo et al. 2021). Other studies suggested that *S. mutans* antigen I/II (Yang et al. 2018), *S. mutans* collagen-binding proteins (Garcia et al. 2021), deletion of the *S.*

mutans delta subunit of RNA polymerase (RpoE) (Xue et al. 2011), *C. albicans*-derived polysaccharide biofilm matrix (Khoury et al. 2020), or the presence of alkaloid nicotine (Liu et al. 2017) can boost the *C. albicans*-*S. mutans* cross-kingdom biofilm formation. Furthermore, the new critical role of *C. albicans* in inducing oral microbial dysbiosis that exacerbates the pathogenesis of root caries has been reported (Du et al. 2021) and the new cross-feeding mechanism between *S. mutans* and *C. albicans* has been suggested with the aid of multi-omics analyses (Ellepola et al. 2019). Other than *C. albicans*-*S. mutans* biofilms, cross-kingdom interactions of *C. albicans* with *Actinomyces viscosus* also significantly increased the cariogenic virulence of biofilm (Deng et al. 2019a). Although some antagonistic interactions between *C. albicans* and *S. mutans* regarding inhibition of *C. albicans* hyphal formation have been reported (Jarosz et al. 2009, Vílchez et al. 2010), it appears that most cross-kingdom interactions facilitate biofilm accumulation while increasing the acidogenicity of biofilm, amplifying the virulence of biofilms.

Denture stomatitis

Denture stomatitis is an inflamed condition of the oral mucosa that is directly in contact with dentures. Although *C. albicans* has been extensively studied as the sole main etiological factor of denture stomatitis, recent studies revealed that cross-kingdom interactions between *C. albicans* and bacteria often prosper in denture biofilms. For example, several studies reported frequent isolation of *C. albicans* with *S. aureus* or *S. epidermidis* from the oral mucous of patients wearing dental prostheses (Tawara et al. 1996, Baena-Monroy et al. 2005, Peters et al. 2010, Pereira et al. 2013). In another study, *Fusobacterium nucleatum* as well as *F. nucleatum subsp. animalis* and *vincentii* were exclusively detected in high numbers with *C. albicans* from denture stomatitis patients (Shi et al. 2016). A recent profiling study demonstrated that a gram-positive anaerobe *Scardovia* showed a positive correlation with *C. albicans* from plaque formed inside of a denture, while three anaerobes (*Leptotrichia*, *Lachnoanaerobaculum*, and *Moryella*) showed a negative correlation (Fujinami et al. 2021). In addition, cooperative physical and metabolic processes among *C. albicans*, *S. oralis*, and *Actinomyces oris* were found to contribute to early biofilm formation on denture material from *in vitro* model (Cavalcanti et al. 2016a). Similar to the findings from the dental caries study (Liu et al. 2017), the effect of nicotine is also appeared to increase the coaggregation of *C. albicans* and *S. mutans* in denture biofilm (Ashkanane et al. 2019).

Periodontitis

Periodontitis is caused by an imbalance between the microbiota and immune defense that results in the loss of soft-tissue seal around teeth, formation of periodontal pockets, and subsequent bone destruction (Buduneli et al. 2011, Lamont et al. 2018, Jabri et al. 2021). While various microorganisms have been known to be associated with the initiation and progression of the periodontitis, red complex, *P. gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, as well as *Aggregatibacter actinomycetemcomitans* have been considered the most pathogenic bacteria involved in periodontitis (Teles et al. 2013). Lately, the role of yeast and its cross-kingdom interaction with various bacteria in periodontitis pathogenesis were discussed. Investigation of the associations of *Candida* and periodontopathic bacteria from seniors (≥ 60 years old) demonstrated that the surface

area of inflamed periodontal tissue was significantly greater when *Tannerella forsythia* and *Treponema denticola* were detected together with *C. albicans* from patients (Shigeishi et al. 2021). Also, several studies revealed various interaction mechanisms between *C. albicans* and *P. gingivalis*. For example, fungal cell adhesins Als3 and Mp65, aspartic proteases Sap6 and Sap9, and protein enolase appeared to mediate the direct physical contact with *P. gingivalis* (Bartnicka et al. 2019). Particularly, *C. albicans* Als3 directly interacted with *P. gingivalis* InlJ, acting as an adhesin-receptor system for *C. albicans-P. gingivalis* association (Sztukowska et al. 2018). Similarly, *C. albicans* surface mannoprotein Flo9 and *F. nucleatum* outer membrane protein RadD were involved in interspecies co-adherence (Wu et al. 2015). In other studies, it showed that virulence factors of *P. gingivalis* such as cysteine proteases and peptidylarginine deiminase enzymes played a crucial role in *C. albicans-P. gingivalis* association (Karkowska-Kuleta et al. 2018, Karkowska-Kuleta et al. 2020). As an environmental factor affecting *C. albicans-P. gingivalis* association, heme, an important iron source for both species, was shown to enhance the pathogenic potential of *P. gingivalis* while interacting with *C. albicans* (Guo et al. 2020). Such *C. albicans-P. gingivalis* association facilitated the invasion and infection of gingival tissue cells (Tamai et al. 2011, Bartnicka et al. 2020), and hampered wound closure (Haverman et al. 2017).

Peri-implantitis

Osseointegrated dental implants have become a clinical standard for replacing missing teeth (Nickenig et al. 2008, Johannsen et al. 2012, Park et al. 2020). The inflammatory response of the gingival tissue around implants represents a growing challenge as many studies demonstrated a high incidence of peri-implant diseases after implantation (Atieh et al. 2013, Gomes et al. 2015, Papathanasiou et al. 2016, Gurgel et al. 2017, Lee et al. 2017). Such peri-implant diseases could lead to destructive failures, resulting in discomfort, painful and costly surgical replacement of failed implants, and the potential breakdown of overall oral health (Charalampakis et al. 2012, Sakka et al. 2012, Rosen et al. 2013). The microbiota linked to dental implant failure has been shown to be associated with a higher prevalence of periodontal pathogens, such as *P. gingivalis*, *Prevotella intermedia*, *Fusobacterium spp*, as well as gram-negative cocci, together with *Candida spp* (Alcoforado et al. 1991, Leonhardt et al. 1999, Hultin et al. 2002, Canullo et al. 2015). While the mechanistic investigation of cross-kingdom interaction between Candida and bacteria on peri-implantitis has been limited, there are some studies describing their implications. For example, one study demonstrated the mutualistic relationship between *C. albicans* and mitis group streptococci (i.e., *Streptococcus mitis*, *Streptococcus sanguinis*, *S. oralis,* and *S. gordonii*) promoted biofilm formation on titanium surfaces, resulting in increased tissue damage (Souza et al. 2020). Another study demonstrated similar findings that mutualistic *C. albicans-S. gordonii* cross-kingdom interactions enhanced biofilm formation and fostered a high level of resistance to combination therapy with antifungal and antibacterial drugs (Montelongo-Jauregui et al. 2018). In addition, there was a study aimed at evaluating the interaction between *C. albicans* and *Streptococcus salivarius* biofilms developed on titanium surfaces, under reduced oxygen levels (Martorano-Fernandes et al. 2020). Unlike their antagonistic relationship observed in oral candidiasis models (Ishijima et al. 2012, James et al. 2016), the presence of *S. salivarius* did not affect fungus growth or *C. albicans* virulence in the context of peri-implant disease (Martorano-Fernandes et al. 2020). Interestingly,

virulence factors of *C. albicans* expressed in biofilms formed on titanium (i.e., expression of genes associated with adhesins and hydrolytic enzymes) significantly varied depending on associated bacterial species (e.g., *S. sanguinis*, *S. mutans*, and *P. gingivalis*) (Cavalcanti et al. 2016b).

Oral cancer

Oral cancer is one of the most prevalent cancers which mainly occurs in the squamous cells (Pushalkar et al. 2011, Arzmi et al. 2019). While various risk factors for oral cancer are known, including tobacco use, heavy alcohol consumption, and human papillomavirus infection, microbial infections also can contribute to its pathogenesis (Arzmi et al. 2019). In particular, *C. albicans* is considered one of the major microorganisms contributing to oral cancer development, potentially promoting carcinogenesis via several mechanisms (Kaźmierczak-Siedlecka et al. 2020). For instance, cross-kingdom interactions of *C. albicans* with oral bacteria *A. naeslundii* and *S. mutans* enhanced invasion of oral squamous cell carcinoma and increased the expression of cancerous inflammatory cytokines, which promoted oral carcinogenesis (Arzmi et al. 2018). Also, metabolites from *C. albicans-S. aureus* cross-kingdom biofilm promoted changes in proto-oncogenes and cell cycle gene expression in normal and neoplastic oral epithelial cell lines (Amaya Arbeláez et al. 2021). It is worth noting that those cross-kingdom interactions are not only involved in the pathogenesis of oral cancer but also cause catastrophic complication. During cytotoxic chemotherapy, the dysbiotic state is often promoted, elevating the risk of oral candidiasis, which results in infectious complications that are a common cause of morbidity and mortality in cancer patients (Bertolini et al. 2019). This was proposed whereby the mutualistic relationships between *C. albicans* and *Enterococcus faecalis* facilitate their overgrowth, which augments mucosal barrier breach by releasing proteolytic enzymes and enhancing virulence gene expression by *C. albicans* (Bertolini et al. 2019).

Combined, cross-kingdom interactions between *C. albicans* and oral bacteria are widely associated with the virulence of various oral diseases. Thus, their mechanism of action should be further understood to successfully manage Candida-involved complex biofilm-associated oral diseases. Further investigations using clinically relevant ecological biofilm models combined with powerful analytical tools may progress our knowledge to the next level.

Therapeutic approaches for Candida-bacterial biofilm-associated oral diseases

Given the aggressive damage caused by cross-kingdom consortia that develop hard-to-remove and highly drug-resistant biofilms, there is a great need to strategically develop cost-effective and safe therapies to prevent cross-kingdom interactions and subsequent biofilm development. While there have been endeavors to develop therapeutic strategies to treat pathogenic bacterial biofilms, targeting fungal-involved polymicrobial biofilms has been limited. Since fungal-bacterial biofilms exhibit dynamic inter-kingdom interactions and diverse drug resistance patterns (Orazi et al. 2019, Khan et al. 2021), efficacies of antibiofilm agents are often limited. Here, the use of naturally derived bioactive molecules,

chemically synthesized compounds, nano-formulated drugs, alternative biofilm treatment strategies as well as antibiofilm surfaces aimed at targeting Candida-bacterial biofilms are summarized (also illustrated in Figure 3).

Natural antibiofilm products

A variety of natural antibiofilm agents derived from medicinal plants have been introduced due to their unique characteristics such as low toxicity, high biocompatibility, and low manufacturing cost. Among them, a portion of bioactive molecules exhibits antibiofilm activities that can target different stages of cross-kingdom biofilm development. For example, cajuputs candy was able to inhibit *C. albicans* hyphal transformation and suppress insoluble glucan formation by *S. mutans* (Septiana et al. 2019). Similarly, the use of curcumin concomitantly downregulated glucosyltransferase and quorum sensing-related gene expression of *S. mutans* as well as the ALS family of *C. albicans* (Li et al. 2019). Other natural compounds extracted from Cranberry (Philip et al. 2019), green tea (Farkash et al. 2019), *Rhamnus prinoides* (Campbell et al. 2020), *Camellia japonica* and *Thuja orientalis* (Choi et al. 2017), olive oil (Arias et al. 2016) as well as *Casearia sylvestris* (Ribeiro et al. 2019) have been also reported to exert antibiofilm activity against *C. albicans-S. mutans* cross-kingdom biofilms. In regards to other Candida-bacterial biofilms, gymnemic acids, isolated from *Gymnema sylvestre*, prevented the development of *C. albicans-S. gordonii* biofilm by inhibiting *S. gordonii* binding to *C. albicans* hyphae (Veerapandian et al. 2019).

Synthetic antibiofilm products

To improve the efficacy and equip diverse functions, extensive efforts have been made to develop chemically synthesized antibiofilm agents. Synthetic antimicrobial peptide (AMP) is one of the widely applied chemically synthesized antibiofilm agents, mainly used to target monospecies biofilm. Recently, however, cyclic dipeptides have been shown to inhibit *S. mutans* and *C. albicans* adhesion to a hydroxyapatite disc, thereby preventing their cross-kingdom biofilm formation (Simon et al. 2019). In addition, cholic acid-peptide conjugates (Gupta et al. 2019), ceragenins (Hacioglu et al. 2019), and guanylated polymethacrylates (Qu et al. 2016), which are synthetic compounds mimicking AMP, have shown to be effective in disrupting *C. albicans-S. aureus* biofilms. Ceragenins were also tested against *C. albicans* cross-kingdom biofilms with *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, or *Klebsiella pneumoniae*, exhibiting its superior efficacy to naturally occurring AMPs (Hacioglu et al. 2020). Other synthetic compounds include nitrochalcone (Bombarda et al. 2019) and peroxynitric acid solution (Iwaki et al. 2020) that were effective against *C. albicans-S. mutans* biofilm, which outperformed broad-spectrum antimicrobial agent chlorohexidine with less cytotoxicity. There also have been attempts to combine synthetic compounds and a classic anticaries agent such as fluoride. Sodium trimetaphosphate accompanied with fluoride elevated pH of *C. albicans-S. mutans* biofilm close to the neutral values, which may reduce the tooth demineralization (Cavazana et al. 2020). The combinations of tt-farnesol and 4'-hydroxychalcone were effective against preformed *C. albicans-S. mutans* biofilm when combined with fluoride (Lobo et al. 2021). Other various combination therapies involving multiple synthetic and natural compounds have also demonstrated enhanced antibiofilm efficacy against cross-kingdom biofilms. Povidone-iodine and fluconazole combination treatment inhibited the

production of α-glucan by *S. mutans* and enhanced fluconazole efficacy against *C. albicans* (Kim et al. 2018). Eugenol with fluconazole or azithromycin also exhibited enhanced antibiofilm activity against *C. albicans-S. mutans* biofilm (Jafri et al. 2020). In addition, 2-aminobenzimidazole with curcumin (Tan et al. 2019), berberine and amphotericin B (Gao et al. 2021), anidulafungin and tigecycline (Rogiers et al. 2018), and fluconazole and minocycline (Li et al. 2015) were effective in deterring *C. albicans-S. aureus* biofilm. Interestingly, some antifungal agents are repurposed to treat *C. albicans* involved cross-kingdom biofilms. For example, voriconazole, a second-generation broad-spectrum triazole antifungal drug, was found to regulate the ergosterol pathway that is critical for the interaction of *C. albicans* and *A. viscosus* (Deng et al. 2019b).

Nanotechnology-based antibiofilm products

While several natural and synthetic biofilm agents exhibit potent antibiofilm activity, their efficacy is often hampered by the limited penetration of these drugs into dense biofilms. To address this issue, recently nanotechnology-based biofilm eradication strategies have been extensively applied to enhance drug penetration and delivery (Besinis et al. 2015, Koo et al. 2017, Benoit et al. 2019, Liu et al. 2019). However, these were mainly tested against monospecies biofilms, and utilization of bioactive nanoparticles to deter cross-kingdom biofilms has been very limited. Encouragingly, one study reported that 20–30 nm-sized chitosan nanoparticles reduced the viability of *C. albicans* and *S. mutans* as well as biomass of the cross-kingdom biofilm (Ikono et al. 2019). More recent studies also demonstrated that loaded curcumin on chitosan nanoparticles (Ma et al. 2020) and positively-charged silver nanoparticles (Lara et al. 2020) exhibited excellent antibiofilm activity against polymicrobial biofilms of *C. albicans* and *S. aureus*. Another study using nanoemulsion containing a quaternary ammonium salt also revealed that it effectively inhibited adherence of *C. albicans*, *S. mutans*, *Lactobacillus casei*, and *A. viscosus* to glass surfaces and subsequent biofilm formation by combinations thereof (Ramalingam et al. 2012).

Alternative antibiofilm strategies

In spite of the advent of such diverse pioneering antibiofilm approaches, antimicrobial resistance and off-target effect due to broad-spectrum antimicrobials demand searching for alternative biofilm treatment strategies. As consequence, the use of probiotic bacteria to suppress pathogenic strains has been suggested as an alternative strategy for controlling oral biofilms (Söderling et al. 2011, Saha et al. 2014). Among them, the effect of *Lactobacillus* genus against *C. albicans-S. mutans* biofilms has been mainly investigated. Interestingly, *Lactobacillus plantarum 108* supernatant (Srivastava et al. 2020) and *Lactobacillus salivarius* (Krzyściak et al. 2017) exhibited capabilities of disrupting *C. albicans-S. mutans* biofilm formation and development while inhibiting the hyphal transformation of *C. albicans*. Furthermore, the use of *Lactobacillus plantarum* CCFM8724 outperformed chlorhexidine in treating and preventing dental caries induced by *C. albicans-S. mutans* biofilm *in vivo* (Zhang et al. 2020). Similarly, antagonizing *Streptococcus parasanguinis* disrupted *C. albicans-S. mutans* biofilm by altering sugar metabolism and glucosyltransferase activity of *S. mutans* (Huffines et al. 2020), which is critical for EPS-matrix development and GtfB-mediated cross-kingdom interaction (Hwang et al. 2017, Kim et al. 2021). Another alternative approach for biofilm eradication is antimicrobial photodynamic therapy (aPDT).

aPDT requires a photosensitizer that generates short-lived cytotoxic reactive oxygen species (ROS) only under stimulating light, enabling localized and time-controlled therapy. A study showed that aPDT therapy using erythrosine as the photosensitizer exhibited a significant antimicrobial effect against biofilm composed of *C. albicans*, *S. mutans*, and *Lactobacillus casei* (Gong et al. 2019). Also, photodithazine- (Quishida et al. 2015a, Quishida et al. 2015b) and curcumin-based aPDT (Quishida et al. 2016) significantly reduced the metabolic activity and total biomass of multispecies biofilms of *C. albicans*, *S. mutans*, and *Candida glabrata*.

Antibiofilm surfaces

Finally, the sharp increase in using dental implants and devices causes a new class of microbially induced infectious diseases via biofilm accumulation on these surfaces (Arciola et al. 2018, Dhall et al. 2021). By recognizing the importance of fungal-bacterial interaction in pathogenic biofilm development, it is crucial to invent infection-resistant biomaterials that can confront polymicrobial biofilms to mitigate the prevalence of microbially induced medical device infections. In this regard, a fluoride-releasing dental prosthesis copolymer was developed that can interrupt polymicrobial biofilm interactions of *C. albicans*, *L. casei,* and *S. mutans* (Yassin et al. 2016). Also, a self-adhesive sealant modified with di-n-butyldimethacrylate-tin showed strong anti-biofilm efficacy against *C. albicans-S. mutans* biofilm neither affects the mechanical properties of the sealant nor causes cytotoxicities (Cocco et al. 2020). While current reports describing the surface that can deal with cross-kingdom biofilms are extremely limited, diverse active biomaterials targeting various mechanisms of action are desired.

Concluding Remarks

As summarized here, polymicrobial biofilms containing *C. albicans* and various pathogenic bacteria together are ubiquitously associated with a variety of oral diseases and have the potential to exacerbate diseases. Therefore, it iterates the importance of expanding biofilm investigations from single-species systems to complex cross-kingdom relationships. Furthermore, it turned out that HIV-infected children are highly susceptible to *C. albicans* associated oral lesions, candidiasis (Charone et al. 2013, Rosa Oliveira et al. 2016, Charone et al. 2017), which is an important marker of immune suppression that may progress to more severe infections with other pathogens. Thus, more vigorous research efforts should be made to develop innovative antibiofilm therapeutics against fungal-associated polymicrobial biofilms. Although several approaches have been introduced to deal with cross-kingdom biofilms, the vast majority is relying on broad-spectrum antimicrobial activity that can kill both fungus and bacterium but lack targeting polymicrobial interactions. A recent binding mechanism-based non-microbicidal approach that intervenes in symbiotic *C. albicans-S. mutans* biofilm interaction suggests a new paradigm in treating cross-kingdom biofilms (Kim et al. 2021). Furthermore, it is worth noting that most of the current therapeutics has been mainly tested using *in vitro* model. A thorough assessment of the efficacy and safety of new therapeutics using an appropriate *in vivo* model should be accompanied for developing successful applications in the prevention and treatment of polymicrobial infections.

ACKNOWLEDGMENTS

This work was supported in part by the National Institutes for Dental and Craniofacial Research (NIDCR) grants DE027970.

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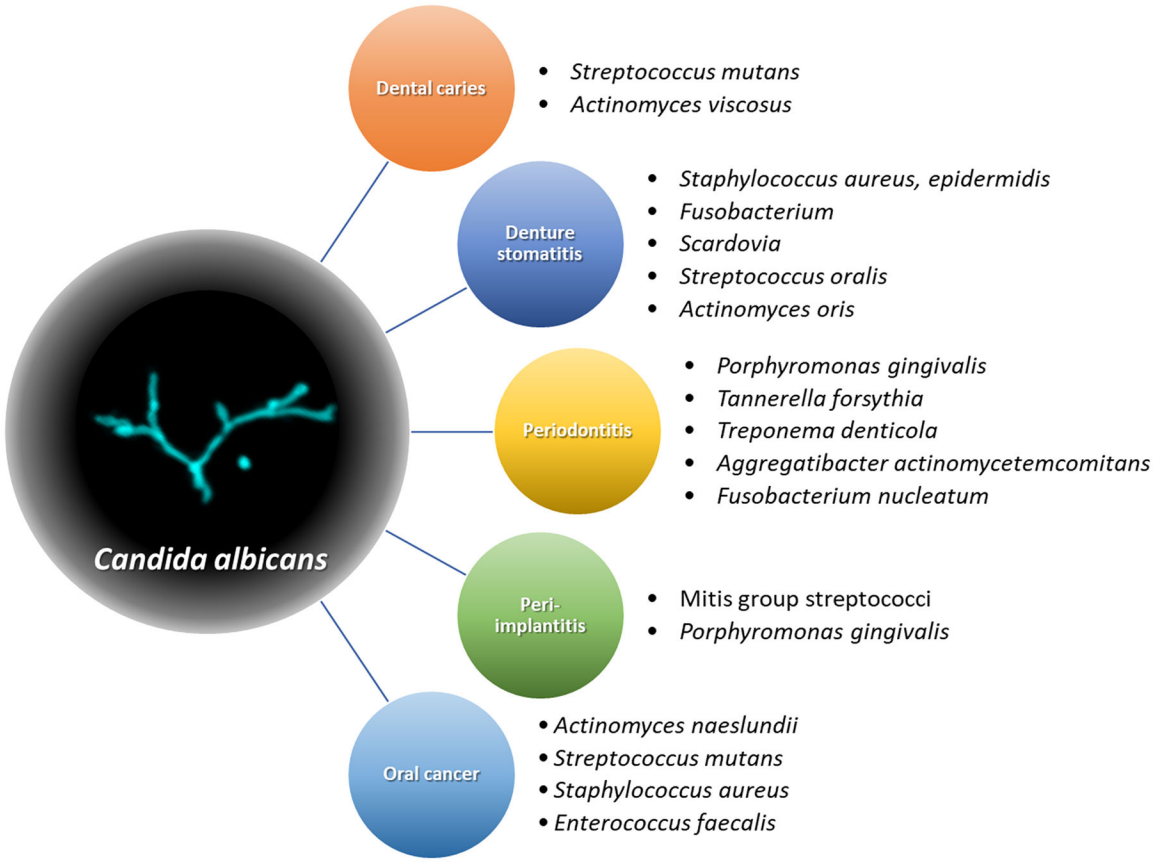

Figure 1.

Association of *Candida albicans* and various bacteria in oral diseases. A variety of gram-positive and -negative oral bacteria interact with *C. albicans*, contributing to virulences of diverse oral diseases ranging from dental caries to oral cancer.

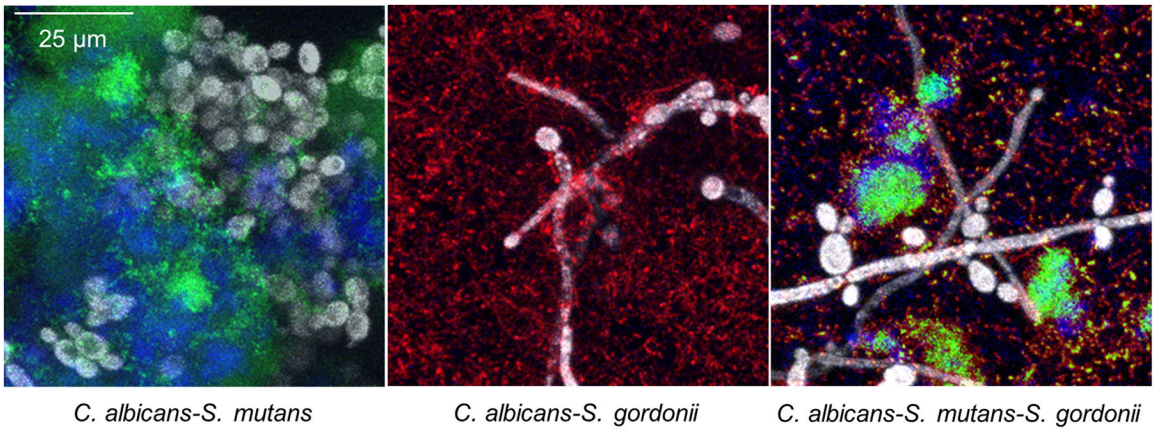

Figure 2.

Representative confocal images of *C. albicans-S. mutans*, *C. albicans-S. gordonii*, and *C. albicans-S. mutans–S. gordonii* biofilms cultured in media supplemented with 1% sucrose. Gray, green, red, and blue colors indicate *C. albicans*, *S. mutans*, *S. gordonii*, and extracellular polysaccharides (EPS)-matrix, respectively. Adapted with permission from Wan et al. (2021) Cross-Kingdom Cell-to-Cell Interactions in Cariogenic Biofilm Initiation. Journal of Dental Research, Vol. 100(1) 74–81. Copyright © International & American Associations for Dental Research 2020

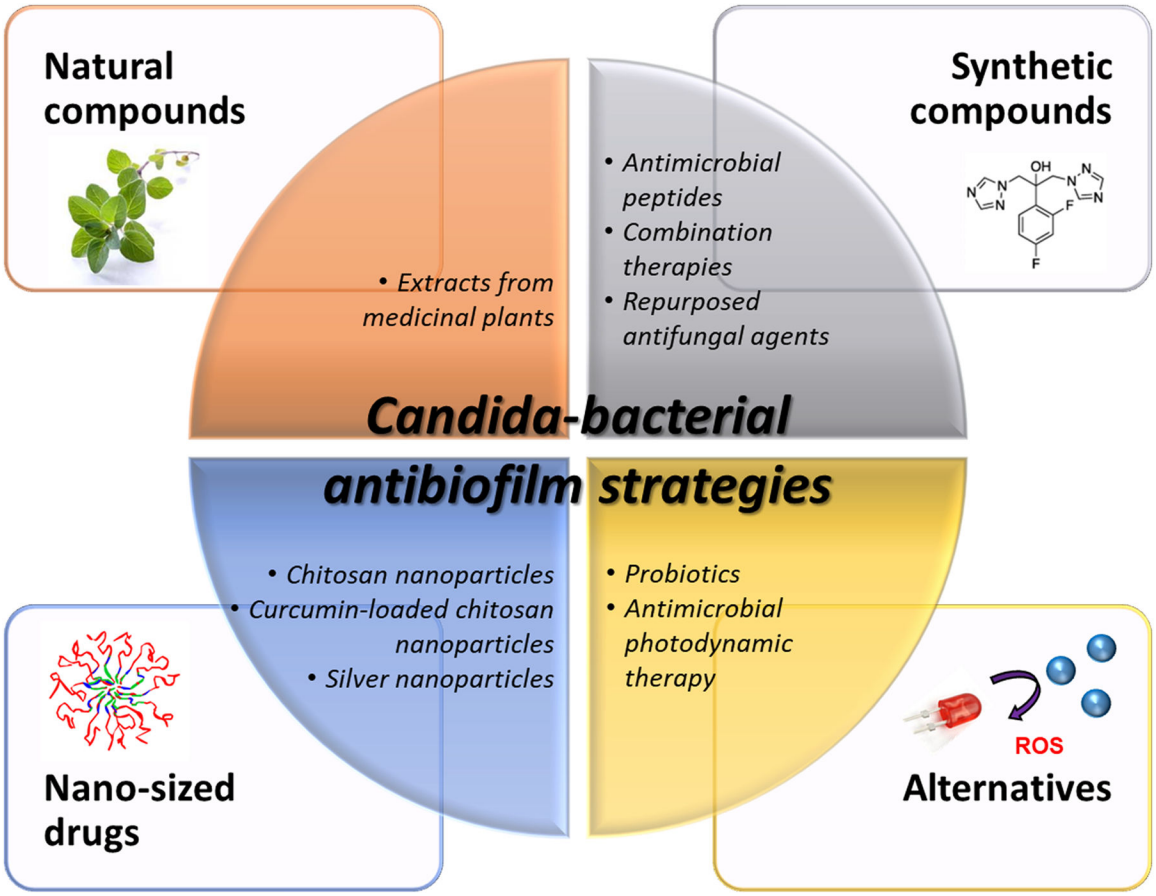

Figure 3.

Various antibiofilm strategies to eradicate Candida-bacterial cross-kingdom biofilm. It includes but is not limited to naturally derived bioactive molecules, chemically synthesized compounds, nano-formulated drugs, and alternative biofilm treatment strategies. ROS denotes reactive oxygen species.