DEMYSTIFYING INTERACTIONS BETWEEN MICRO ORGANISMS IN ORAL CANDIDIASIS BIOFILM: THE KEY TO ENHANCING TREATMENTS

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Palavras-chave: *Candida albicans*. *Streptococcus*. Candidíase Bucal.

RESUMO

Introdução: *candida albicans* é um patógeno fúngico que pode provocar doenças que variam de infecções orais a distúrbios sistêmicos com risco de vida. Hoje se reconhece que as bactérias orais, como o gênero *Streptococcus*, estabelecem relações sinérgicas com *C. albicans*, o que pode potencialmente aumentar a virulência e patogenicidade do fungo. **Objetivo:** esta revisão narrativa teve como objetivo discutir os mecanismos de interação *Candida-Streptococcus* e sua contribuição para o agravamento da candidíase oral. Além disso, fornece uma breve explanação sobre a formação do biofilme e potenciais alvos terapêuticos. **Fonte dos dados:** foi realizada pesquisa na base de dados Pubmed para a busca de artigos publicados em Inglês até maio de 2022. Para isso, foram utilizados descritores relacionados ao tema. Estudos *in vitro* foram selecionados, tabulados e seus resultados quantitativos e qualitativos analisados descritivamente. **Síntese dos dados:** entre as bactérias denominadas colonizadores iniciais, evidências apontam que *S. gordonnii* e *S. oralis* têm implicações importantes na candidíase oral, na qual biofilmes mistos aumentam a gravidade da infecção e desafiam a defesa do hospedeiro. Por outro lado, os desfechos das interações entre *C. albicans* e *S. mitis*, *S. sanguinis* ou *S. mutans* permanecem pouco explorados no cenário da candidíase oral, apesar de evidências apontarem um aumento dapopulação fúngica e de fatores de virulência. **Conclusão:** de maneira geral, considerando o perfil polimicrobiano da infecção e o potencial agravamento das doenças provocadas por *Candida* spp, as estratégias terapêuticas não devem estar focadas apenas no fungo, mas também devem considerar o manejo da bactéria.

Keywords: *Candida albicans*. *Streptococcus*. Oral Candidiasis.

ABSTRACT

Introduction: c*andida albicans* is a fungal pathogen that can provoke diseases ranging from oral infections to life-threatening systemic disorders. It is now recognized that oral bacteria, such as the genus *Streptococcus*, establish synergistic relationships with *C. albicans*, which could potentially increase the fungi's virulence and pathogenicity. **Objective:** this narrative review aimed to discuss the *Candida-Streptococcus* mechanisms of interactions and their contribution to increasing oral candidiasis severity. In addition, it provides a background of biofilm formation and potential therapeutical targets. **Sources of Data:** searches for papers in English were performed in the Pubmed database until May 2022. MeSH and free terms related to the field were used. *In vitro* studies were selected, tabulated, and qualitative and quantitative data were analyzed descriptively. **Synthesis of Data:** among the early colonizers bacteria, evidence pointed out that *S. gordonnii* and *S. oralis* have major implications in oral candidiasis, in which mixed biofilms increase the infection severity and challenge the host's defense. On the other hand, the outcomes of the interaction between *C. albicans* and *S. mitis*, *S. sanguinis,* or *S. mutans* remain little explored in the oral candidiasis scenario, albeit evidence pointed out an enhanced fungus population and virulence factors. **Conclusion:** overall, considering the polymicrobial profile of the infection and the potential to increase *Candida*-related disease severity, therapeutical strategies should also consider bacteria management.

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INTRODUCTION

The oral microbiome comprises around 700 species that can form highly organized structures known as biofilms.[1] Biofilms are communities of microorganisms that are bound to each other, creating a multilayer scaffold adherent to biotic (e.g., oral epithelium) or abiotic (e.g., dentures) surfaces.[2] These aggregates of microorganisms are surrounded by an extracellular matrix of polymeric substances (EPS), forming a local microenvironment that protects the biofilm against external agents, such as an antimicrobial agent or an immune attack.[3] This is problematic because these complex and dynamic structures can cause oral infections that are highly prevalent, leading to public health issues worldwide.[4]

One of these infections is oral candidiasis, a disease characterized by asymptomatic white or red lesions in the oral mucosa. This disease is prevalent in the elderly, infants, immunosuppressed individuals, and denture users.[5] Although oral Candidiasis symptoms are usually amenable, the infection is a life-threatening problem that could lead to systemic infections and even death.[5] In this scenario, it is well known that in oral Candidiasis biofilm, the fungi *Candida albicans* is the predominant microorganism.[6] However, in recent years, it has been recognized that some bacteria commonly found in the mouth, such as the genus *Streptococcus* spp.[7] could interact with *C. albicans*, establishing a partnership known as synergism.[8] This beneficial relationship can increase the severity and frequency of oral Candidiasis lesions,[9] which could challenge the antifungal therapies solely focused on the fungi.

Over the past decades, the available treatments for oral candidiasis have been ineffective because they don't have a therapeutic target and do not consider the biofilms' bacteria counterparts.[8,10,11] Consequently, this lack of effectiveness leads to recurrent and severe systemic conditions with mortality of around 25%.[12] This alarming number has been prompting researchers to understand the molecular mechanisms of biofilm formation and its interactions. Hence, this background will provide potential targets for treating oral candidiasis infections.[13] In addition, comprehending that the oral candidiasis biofilm is not exclusively composed of fungi is the key to offering additional strategies to control the disease,[8] such as reducing dietary sugar intake. Taken together, the knowledge of biofilm formation and its interactions could link basic science to clinical practice.

Several reviews have discussed the synergistic relationship between *C. albicans* and bacteria of the genus *Streptococcus.*[4,8,11,14,15] Yet, almost all of them exclusively focused on the bacteria perspective,[8,14,15] like how the fungi could enhance the severity of dental caries; at the same time, the oral candidiasis viewpoint has remained less explored.

The present narrative review discusses the *Candida-Streptococcus* mechanisms of interactions and their contribution to increasing oral candidiasis severity. Nonetheless, prior to discussing it, this review also demystifies biofilm formation, the *C. albicans* life-cycle, and its ability to cause the disease to provide a background for understanding many interaction mechanisms. Lastly, it discusses state of the art potential therapeutical targets during biofilm formation and its interactions.

SOURCES OF DATA

Searches were performed in the Pubmed database to retrieve papers published in English before May 2022. Thus, scientific research of *in vitro* studies exploring interactions among *C. albicans* and *Streptococcus* bacteria presenting qualitative or quantitative data were selected. For this, MeSH terms such as *Candida albicans* and *Streptococcus* were used. In addition, free terms related to the field were established. Then, boolean operators (OR, AND) combined those search terms. Finally, hand searching was also performed in the papers chosen initially in the reference list.

Subsequently, duplicates were thrown out. Then, abstracts were read. Papers that do not include data about *Candida-Streptococcus* interactions were excluded. Lastly, 30 full texts were summarized in an Excel worksheet, and the findings were synthesized.

SYNTHESIS OF DATA

How is biofilm formed?

Typically, an oral biofilm formation comprises four phases: i) adhesion, ii) proliferation, iii) maturation, and iv) dispersion[3] (Figure 1). During the adhesion phase, free-floating (planktonic) cells initially attach to a surface (e.g., teeth, dentures, oral epithelium) coated with a salivary pellicle.[16] Some bacteria known as early colonizers (*Streptococcus gordonii, Streptococcus mitis, Streptococcus oralis,* and *Streptococcus sanguinis*) bind to salivary receptors as mucins, proline-rich protein, and α-amylase.[17,18] This preliminary attachment establishes a basal layer of cells that will anchor other bacteria species called late colonizers, promoting a coadhesion between them.[18,19] Interestingly, these adhesion-binding processes are mediated by tiny components in the microorganisms' cell walls, known as adhesins.[18,19]. Thus, these adhesins could fit each other and establish a selective binding among the microorganisms.

Following formation of a basal cell layer, the sequence of events proceeds to its proliferation. Then, the microorganisms interact even more, multiply, and begin to produce an EPS extracellular matrix.[3] Finally, after increasing its population and producing a matrix, the biofilm starts to mature in the third phase, and the matrix reaches a complex three-dimensional structure that physically protects the biofilm.[3,20] Besides protection, the matrix provides the biofilm a microenvironment with different pH gradients and nutrient availability.[21] In this environment, polymicrobial interactions

find ideal conditions to cooperate (synergism) to enhance their population or compete (antagonism) for nutrients.[22] Importantly, when the biofilm is mature, this condition enables the biofilm to be pathogenic, or in other words, to cause oral infections and diseases.[3]

Finally, in the last stage, the microorganisms slowly disperse from the biofilm as planktonic cells to colonize new niches, or advance with the infection in cases of the disease.[23]

C. albicans life cycle

A relevant feature of *C. albicans* is its ability to switch among different morphologies (cell types) during biofilm formation, comprising yeast cells, oval pseudohyphal cells, and elongated hyphal filamented cells[24] (Figure 2). In general, yeast cells are involved in the adhesion phase, whereas an early-stage filamentation (pseudohyphae) starts during proliferation. During the maturation phase, *C. albicans* forms several elongated hyphal filaments, interconnecting each other, providing a complex structure to the biofilm.[3] In addition to creating this scaffold, the hyphae are considered a virulence factor due to their capacity to cause the disease.[25] In the hyphae form, *C. albicans* can induce endocytosis or actively penetrate host cells,[6] as described below.

After 24 hours, under a microscope, a mature biofilm comprises a basal layer of cells containing yeasts and pseudohyphae, followed by a second layer of several interlaced hyphae (Figure 3A). Macroscopically, a mature biofilm seems robust by developing a dense and opaque appearance on a surface (Figure 3B).

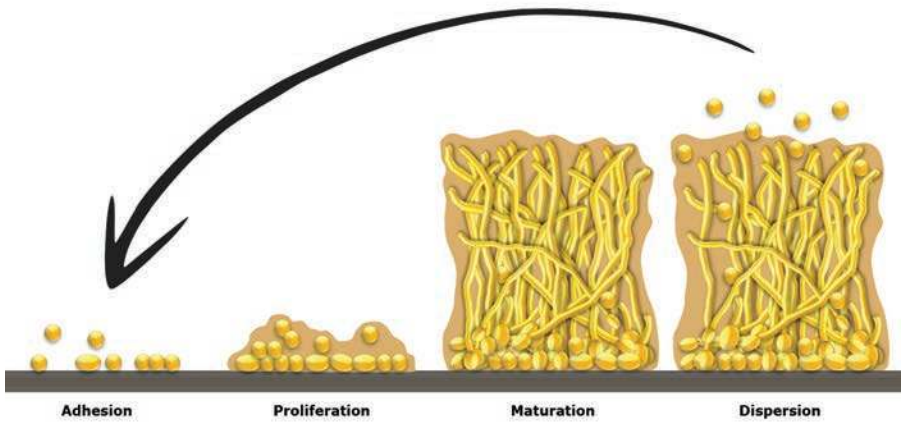

***Figure 1**: Stages of biofilm formation represented by cells of C. albicans. i) adhesion (cells attached to a surface and coadhesion between them; ii) proliferation (multiple interactions among the cells and beginning of EPS extracellular matrix production; iii) complex three-dimensional structure of cells and matrix; iv) dispersion (cells start to disperse to colonize new niches).*

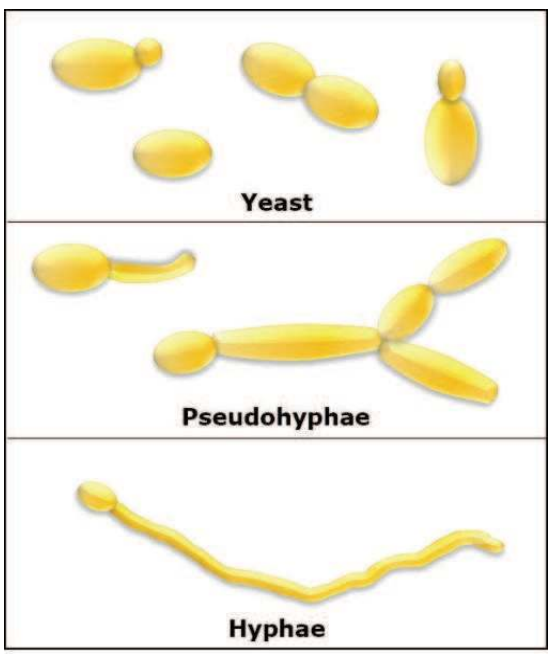

***Figure 2**: C. albicans morphology comprises yeast (oblong-shaped cells); short or long pseudohyphal cells (oval-shaped with a constriction at the bud neck); hyphae (elongated filaments with parallel sides along their entire length and no constrictions).*

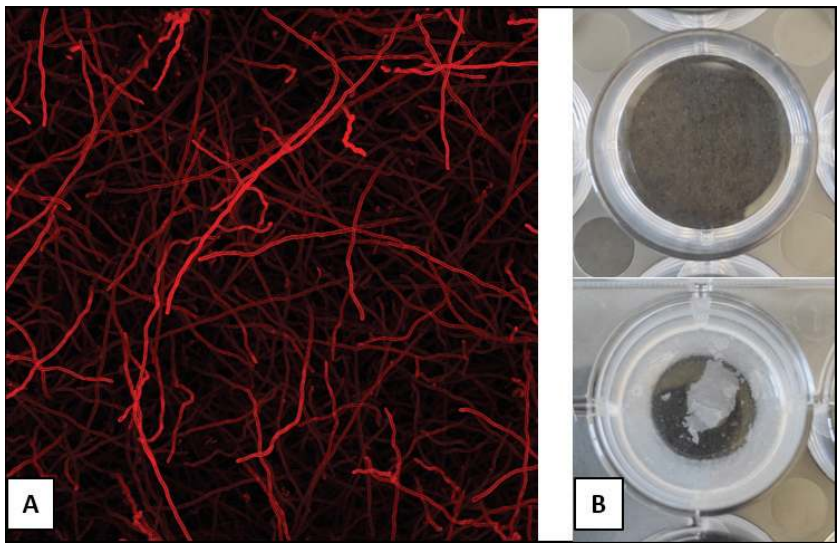

***Figure 3**: Representative images of a C. albicans biofilm formed on 12-well polystyrene plates. A) Several C. albicans hyphae form a complex tangle of cells on a confocal microscopy view. B) Macroscopically, a surface without biofilm compared to a surface coated with a dense and opaque layer.*

C. albicans pathogenicity mechanisms: from healthy to diseased

Candida albicans is a commensal fungus that is typically harmless to the host. However, these fungi can become trick opportunistic and cause infections under imbalance behaviors in the host, such as immunosuppression.[6] Under such conditions, *C. albicans* can invade the epithelial cells by active physical penetration or internalization (endocytosis).[6] In the first process, *C. albicans* can disassemble epithelial cell junctions to penetrate the tissues, yet these mechanisms remain unclear.[26] On the other hand, in the internalization process, cell-surface proteins (adhesins) expressed in the fungi cell wall, such as Als3 and Ssa1, can mimic epithelial cell junctions to induce fungi endocytosis.[26,27] Although Als3 and Ssa1 have a significant role in this process, other adhesins also bind to host epithelial cells to enable *C. albicans* to invade the tissue, such as agglutinin-like sequence (ALS) proteins (Als1-Als7 and Als9), Hpw1 and, secreted aspartyl proteinases (Saps).[26,27] Thereby, adhesins are relevant not only for mediating interactions among microorganisms, as previously mentioned, but also for *C. albicans'* pathogenicity.

Candida-Streptococcus interactions

C. albicans can interact with many microorganisms in the oral cavity. Among them, the initial colonizers (*Streptococcus gordonii, Streptococcus mitis, Streptococcus oralis,* and *Streptococcus sanguinis*) and *Streptococcus mutans* are recognized for their ability to co-aggregate with *C. albicans* to potentially promote interkingdom virulent interactions.[28] Here, we will overview each partnership interaction pathway and its implications on oral candidiasis disease.

C. albicans and *S. gordonii*

Streptococcus gordonii is frequently associated with *C. albicans* in biofilms on dentures.[29] So far, the interactions among them have been explored more mainly due to their potential to increase disease severity[30] and contribution to challenging the host defense as well as therapies.[31-33]

The interactions among these microorganisms occur via physical contact or chemical communication (quorum-sensing).[31] In the first process, *in vitro* observations have shown that bacteria attachment on the fungi surface does not occur in the entire *C. albicans* cell wall.[30] Thereby, fungi-bacteria binding is a heterogeneous process that occurs via specific adhesins, similar to fitting pieces in a puzzle. It is well established that some bacterial components such as SspB of the antigen I/II family of polypeptides, glucosyltransferase G (GtfG), and the comCDE operon can bind to fungi adhesins (Als3, Eap1, and Hwp1), establishing selective binding pathways.[34,35] Remarkably, these *C. albicans* adhesins were usually expressed in hyphae,[32,36,37] so it was firmly believed that *S. gordonii* could only bind to *Candida* as an elongated form. However, evidence showed that the bacteria could also attach to yeast, albeit less frequently.[31] Notwithstanding, this physical interaction among *C. albicans* and *S. gordonii* induces fungi filamentation, increasing biofilm biomass two-fold.[30]

Another interaction pathway among *C. albicans* and *S. gordonii* is a kind of "cellular communication" known as quorum-sensing.[31] This process occurs through small chemical molecules or metabolic subproducts produced by microorganisms at high population densities. Thus, these

chemical compounds are extracellularly released, modulating the microorganism's life cycle or virulence.[38,39] Evidence has shown that *S. gordonii* supernatants alone (i.e., only metabolic subproducts, not cells) can promote interactions with *C. albicans*, enhancing the fungi biomass.[32] In addition, autoinducer-2 (AI-2), a common quorum-sensing molecule in Streptococcus bacteria,[40] can induce *C. albicans* filamentation,[32] revealing that physical contact is not required to establish this interaction. Taken together, the physical and chemical interactions among *C. albicans* and *S. gordonii* favor the filamentation of fungi, which enhances its ability to cause disease and tissue damage.

In addition to those effects, one of the significant features of the hyphae form is that it also enables *C. albicans* to survive and escape from the host defense. In this process, macrophages engulf *C. albicans* (phagocytosis), and the fungi begin to expand their filaments, resulting in macrophage membrane damage and *C. albicans* escape.[32] It was shown that an association between *C. albicans* and *S. gordonii* significantly increases the escape ratio,[32] which could challenge the host defense; consequently, the risk of disseminated candidiasis could be increased. With immune depletion, antimicrobial therapies could potentially control biofilm virulence. Nevertheless, biofilms of *C. albicans* and *S. gordonii* were more resistant to antifungal drugs such as fluconazole, amphotericin B, and caspofungin.[31,33]

Overall, the evidence here indicated that the synergistic relationship between *C. albicans* and *S. gordonii* is an emerging concern during oral candidiasis disease. Therefore, future strategies must also consider the bacterial counterparts in the biofilm.

C. albicans and *S. mitis*

So far, whereas the *C. albicans* interactions with *S. gordonii* is well characterized, the relationship with *S. mitis* is still little explored.[8,42] Bacteria, whose species nominate the early colonizer group, are typically considered harmless microorganisms. Even so, *S. mitis* can cause systemic infections, such as endocarditis and bacteremia.[41]

Notably, during the interactions with *C. albicans*, *in vitro* investigations showed that these microorganisms do not surround each other,[8] possibly leading to a false idea that they do not interact. In fact, these microorganisms could establish beneficial relationships in which genes related to fungi adhesion were upregulated, such as ALS1, ALS3, HWP1, and BCR1.[42] Interestingly, the synergistic interaction between *C. albicans* and *S. mitis does* not reveal a quantitative gain of fungi biomass and population. However, these partnerships qualitatively change the biofilm by increasing *C. albicans* filamentation, shown *in vitro* and *in vivo.*[42] These phenomena could explain the increased tissue damage in *C. albicans* and *S. mitis* biofilms compared to single *C. albicans* in organotypic models of the oral mucosa.[43] Even though *C. albicans* and *S. mitis* interactions potentially contribute to oral Candidiasis severity, as previously mentioned, the pathways of this relationship are still poorly explored. Therefore, future investigations should further explorate those microorganisms' interactions and their impacts on oral candidiasis.

C. albicans and *S. oralis*

Among the mitis group bacteria, *S. oralis* has perhaps the greatest implication in oral candidiasis severity. Such bacteria are highly prevalent in the mouth and frequently associated with cases of septicemia in immunocompromised individuals, a condition known as a risk of factor to *Candida* infections.[44]

The synergism among *C. albicans* and *S. oralis* benefits the bacteria to increase its population ~10 fold and biomass ~45 fold.[44] Meanwhile, *C. albicans* do not increase their quorum but form higher amounts of elongated hyphae in the presence of *S. oralis.*[44,45] In the first two hours of fungi-bacteria interactions as planktonic (free-floating) cells, over half of *C. albicans* cells were in the hyphae form with *S. oralis* surrounding it, as well as attached to it.[46] To better understand the mechanisms of *C. albicans* filamentation during the *S. oralis* interaction, six master regulators that control the *C. albicans* biofilm development were evaluated.[45] These regulators (Bcr1, Efg1, Tec1, Ndt80, Rob1, and Brg1) integrated a complex expression circuit of genes that control biofilm formation.[47] Surprisingly, only Efg1 has a role during the *S. oralis* relationship, suggesting that filamentation is critical for establishing this interaction.[45] In addition to the master regulators, the expression of genes related to adhesion such as ALS1, ALS3, and HWP1 was also evaluated, with ALS1 being upregulated in the presence of bacteria.[45]

As previously mentioned in this work, *C. albicans* can invade the oral epithelium in the hyphae form.[6] However, in the presence of *S. oralis*, this invasive process is ~7 fold higher, in which the entire fungi biomass invades the mucosa deeper through the tissue than a single *C. albicans* infection.[48] Such invasive mechanisms were explored further in murine models.[9,45,48] It was observed that *C. albicans* penetration in the epithelium occurs between the epithelial junctions.[48] Notably, *S. oralis* modulated the epithelial response to the biofilm to be more permissive to invade the tissue. In this process, intercellular junctions, so-called E-cadherin, were cleaved, and *C. albicans* actively penetrated the mucosa.[48] Once inside the tissue. *C. albicans* could reach the bloodstream and disseminate in the host.[49] To test the hypothesis that *S. oralis* could increase fungi spread inside the host, mice co-infected with *C. albicans* and *S. oralis*

showed more fungi in the kidneys than single *C. albicans.*[9,48] Another consequence of the invasive processes is that biofilms of *C. albicans* and *S. oralis* increase the severity and frequency of oral candidiasis lesions in mice.[9]

Although the *S. oralis* implications during the oral candidiasis are well established in both *in vitro* mucosa and murine models, knowledge of host defense is still incipient. In addition, the literature lacks evidence regarding the repercussion of the *C. albicans* and *S. oralis* interaction in current antifungal therapies. Thus, further investigations should explore it.

C. albicans and *S. sanguinis*

Streptococcus sanguinis has shown a potentially antagonistic relationship with *C. albicans.*[50,51] Such an effect is due to quorum-sensing molecules known as diffusible signal factors (DSF),[52] which could inhibit *C. albicans'* adhesion and filamentation ability, as well as decrease fungi biomass.[50] Nevertheless, evidence pointed out that the physical contact between *C. albicans* and *S. sanguinis* does not in fact change the number of hyphae in comparison to solely *C. albicans* biofilms.[42] In addition, *in vivo* models of invertebrates reveal an increase of hyphae in co-infections of *C. albicans* and *S. sanguinis* compared to single *C. albicans.*[42] Taken together, the presence of *S. sanguinis* does not modulate the filamentation of *C. albicans*, yet when in contact with the host, an unknown mechanism favors the hyphae form. It is noteworthy that *C. albicans* and *S. sanguinis* interactions are still poorly investigated, with the bind ligands among these microorganisms being the main unidentified field.

C. albicans and *S. mutans*

Although *S. mutans* is the primary bacteria related to caries lesions,[53] it is now conceivable that the non-related caries microorganism *C. albicans* aids in increasing caries severity.[15,54] *Candida albicans* is frequently found in children with acute caries lesions, a condition is known as Early Childhood Caries (ECC).[15,54] ECC is characterized by rampant caries lesions on the tooth surface of toddlers followed by frequent consumption of dietary sugar.[55] As *S. mutans* and *C. albicans* clearly synergize to accentuate that disease,[56] many investigations have focused on identifying the mechanisms of these fungi-bacteria interactions.

During *C. albicans–S. mutans* biofilm formation, it was observed that *C. albicans* yeasts in the basal layer and clusters of *S. mutans* colonies surrounded it. In this scenario, *C. albicans* hyphae were in the outermost layer coated with higher amounts of EPS.[56,57] Importantly, when *C. albicans* and *S. mutans* interact, the extracellular matrix production heightens significantly, which confers more prominent and thicker biofilms.[56] Furthermore, during the fungi-bacteria interaction, *S. mutans* secrete a so-called exoenzyme glucosyltransferase (Gtfb),[58] which binds heterogeneously to the *C. albicans* surface.[59] Evidence has shown that GtfB has a high affinity for the *C. albicans* mannans, which is a significant part of the *Candida* surface cell wall, being one of the "connections" between *C. albicans* and *S. mutans.*[56,57] Interestingly, in the absence of mannans, Ca-Sm biofilms were easily removed from a surface,[57] suggesting that besides providing binding interactions, this fungi component provides mechanical stability to the biofilm.

Remarkably, the *C. albicans* cell wall is fairly complex with several distinct elements,[60] so it is plausible that *S. mutans* have more affinity for some structures/adhesins than others. However, so far, these other pathways are still little explored, yet some gene expression analysis could guide possibilities. For example, an analysis of up to 6000 genes revealed that *C. albicans* and *S. mutans* biofilms enhanced the expression of genes related to *C. albicans* transcriptional regulation.[61] Thereby, further investigations should explore those transcriptional factors as potential GtfB ligands.

In addition to enhancing the extracellular matrix, Ca-Sm physical interactions increased the biofilm population and upregulated the expression of genes related to hyphae form (HWP1, SAP4, and SAP6).[61,62] In stark contrast, *S. mutans* supernatant inhibits *C. albicans'* hyphae formation.[64,65] This phenomenon of hyphae suppression is due to the competence-stimulating peptide (CSP), a quorum-sensing molecule produced by *S. mutans.*[65] Collectively, this hyphae modulation (positively or negatively) could lead to virulent biofilms. Unsurprisingly, mixed biofilms containing *S. mutans* and other bacteria showed higher invasion, tissue damage, and immune response.[62] However, the literature lacks evidence regarding the biofilm virulence of solely *C. albicans* and *S. mutans*.

It is not conceivable to discourse about *S. mutans* without pointing out the role of dietary sugar. In the presence of carbohydrates (mainly sucrose), *S. mutans* produce structurally robust biofilms leading to tooth demineralization.[66,67] Under the viewpoint of the fungi-bacteria interaction, *C. albicans* does not efficiently metabolize sucrose. Then, *S. mutans* can convert sucrose into monosaccharides for *C. albicans* metabolism, potentially enhancing biofilm pathogenicity.[63] Thereby, considering that patients with denture stomatitis had around 68% of *S. mutans* colonization in the prosthesis and mucosa,[68] clinicians should not only be concerned about sugar intake in young individuals but also patients using dentures as well as with Candida-related life-threatening diseases. Furthermore, clinicians should be concerned about individuals with diabetes or non-controlled glucose levels. Higher glucose levels in the

blood and saliva typically were caused by harmful lifestyles associated with uncontrolled carbohydrate intake.[69] In addition, evidence has shown that in *C. albicans* and *S. mutans* biofilms, elevated amounts of glucose led to robust and potentially more virulent biofilms.[70] Overall, the evidence pointed out that integrative assistance in dietary sugar intake control should also be established in oral Candidiasis care for patients more affected by the infection, such as immunocompromised individuals.

Despite *C. albicans* and *S. mutans* interactions being well understood in ECC behavior, knowledge about the implications of these microorganisms' relationship in the oral Candidiasis scenario remains incipient. Therefore, future studies should consider investigating it.

DISCUSSION

Typically, Amphotericin B, Nystatin, Miconazole, or Fluconazole have been the standard antifungal agents chosen for oral candidiasis infections.[5] However, the microorganisms may have become resistant to those therapies in the past years.[71,72] For that reason, searching for targets has been explored as potential biofilm disruption strategies. Current biofilm-targeting research is based on the *C. albicans* cell wall biogenesis, which impairs cell viability; secondly, based on fungal interactions that may enhance fungal pathogenicity.[73] As *C. albicans* is frequently more virulent in the presence of *Streptococcus* bacteria in the oral environment, knowledge about fungal-bacterial interactions will perhaps contribute significantly to finding therapeutical targets of oral Candidiasis disease.

Notably, *C. albicans* cell wall components such as the adhesins Hwp1, Als1, and Als3 were frequently involved in the early colonizers' interactions.[34,35,42,45,63] In addition, quorum-sensing molecules of *S. gordonii*, *S. sanguinis*, and *S. mutans* could modulate (positively or negatively) *C. albicans'* filamentation.[32,52,63,65] Considering that those mechanisms favor fungal-bacterial biofilm establishment and virulence, they could be used as targets. However, none of these interaction pathways were tested for antifungal therapies to our knowledge. In fact, although the literature has credible evidence about *C. albicans*-bacterial interactions, few studies have explored fungi cell wall components as a target in this context. For example, one study reported that in the absence of glucans and mannans, the *C. albicans* and *S. gordonii* biofilm were more susceptible to Amphotericin B.[31] On the other hand, other cell wall components are still unexplored in *Candida-Streptococcus* biofilms as well as new antifungal drugs.

To date, echinocandins are one class of drugs based on target strategies. These drug agents were represented by caspofungin, micafungin, and anidulafungin; they were approved by the US Food and Drug Administration (FDA) in 2001.[10] Echinocandins could be administered intravenously to treat esophageal and invasive candidiasis in cases of non-response to previous topical strategies.[73] Those drugs target α-1,3-glucan synthesis, a significant constituent of *C. albicans'* cell wall. In the past 20 years, clinical studies have shown high efficaciousness with low resistance.[62] However, despite considerable clinical success with echinocandin use, the *C. albicans* cell wall is a dynamic structure and its composition and organization could vary among the biofilm.[74] Thus, other targets in the cell wall should also be explored.

Apart from that, importantly, oral candidiasis management should also consider the polymicrobial profile of the disease.[4] As fungal-bacteria interactions could increase biofilm virulence, new approaches for candidiasis treatment should also consider bacteria adhesins as targets or include drug agents selective for bacteria. Therefore, considering the oral candidiasis challenge treatment, further studies were encouraged to investigate the bacterial counterparts' strategies.

CONCLUSION

This work discussed *Candida-Streptococcus'* mechanisms of interactions and their implications for oral Candidiasis infections. Clearly, the synergistic interactions among these microorganisms potentially increase the severity of the disease and challenge the current strategies. Thus, researchers and clinicians should consider not only the fungi in candisiasis treatment but also the polymicrobial profile of the infection. Taken together, antimicrobials used for oral candidiasis should also enable bacteria inhibition since these microorganisms have a relevant role in the establishment and progression of the disease. In addition, from a clinical viewpoint, the clinician should be concerned with other approaches to biofilm control, such as the management of dietary sugar intake and effective care for diabetic individuals. Overall, further investigations are encouraged to cast a critical eye over the interactions of *Candida and Streptococcus* and their outcomes.

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