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REVIEW ARTICALE

SYNERGISTIC INTERACTIONS BETWEEN STREPTOCOCCUS MUTANS AND CANDIDA ALBICANS IN ORAL BIOFILMS AND ITS THERAPEUTIC IMPLICATIONS IN DENTAL CARIES: A NARRATIVE REVIEW

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Background: Dental caries is a chronic, multifactorial disease resulting from microbial dysbiosis within the oral biofilm. The persistent colonization and cooperative behavior of specific microbial species contribute significantly to its pathogene
Objective: This review explores the synergistic interactions between Streptococcus mutans and Candida albicans, two prominent oral microorganisms, with a focus on their molecular crosstalk, clinical relevance, and implications for targeted therapy.
Materials and Methods: A narrative synthesis was conducted based on peer-reviewed literature examining the co- pathogenic mechanisms, biofilm dynamics, and emerging anti-biofilm strategies targeting dual-species communities.
Results: Current evidence demonstrates that C. albicans enhances extracellular polysaccharide production by S. mutans through glucosyltransferase activity, promotes glucan-mediated co-adhesion, and modulates virulence gene expression in both organisms. Their co-existence leads to increased biofilm biomass, acidogenic potential, and resilience against conventional antimicrobial measures. These interactions are notably prevalent in early childhood caries and immunocompromised hosts.
Conclusion: The cross-kingdom synergism between S. mutans and C. albicans constitutes a potent pathogenic axis in cariogenesis. Targeted disruption of this alliance through novel therapeutic strategies—such as glucosyltransferase inhibitors, nanoparticle-based antimicrobials, and biofilm-disrupting agents—holds potential for improving caries management, particularly in high-risk populations. Further clinical validation is necessary to translate these findings into effective, personalized interventions.

Keywords: Streptococcus mutans, Candida albicans, oral biofilm, dental caries, early childhood caries, symbiosis

INTRODUCTION

Dental caries remains a globally pervasive non-communicable disease, driven by a dynamic interplay between host factors, diet, and the oral microbiota. Traditionally, the etiology of dental caries was centered on Streptococcus mutans, a gram-positive facultative anaerobe capable of acid production and tolerance. Its pivotal role was solidified by Loesche's "specific plaque hypothesis", which emphasized its contribution to enamel demineralization through lactic acid production following carbohydrate metabolism [1]

However, in recent decades, there has been a paradigm shift from this mono-microbial view to a polymicrobial framework, recognizing the complexity of biofilm-associated diseases. Notably, Candida albicans, a fungal commensal often dismissed as a mere opportunist, has emerged as a co-contributor to cariogenic biofilms[2,3]

The convergence of bacterial and fungal communities termed "cross-kingdom interactions"—has brought attention to their synergistic virulence, particularly in vulnerable populations such as infants and immunocompromised individuals.

Numerous studies have demonstrated that when C. albicans and S. mutans coexist within the oral biofilm, they engage in synergistic behaviors that amplify biofilm density, structural complexity, acidogenicity, and resistance to antimicrobial agents. This interkingdom alliance promotes persistent colonization of tooth surfaces, particularly in high-risk individuals such as young children with frequent sugar exposure, reduced salivary flow, or compromised oral hygiene. Their mutual enhancement of metabolic activity and gene expression creates a microenvironment conducive to the progression of early childhood caries (ECC), a rapidly advancing and often recurrent disease.[4-6]

In light of this evidence, there is a pressing need to understand the molecular, metabolic, and clinical dimensions of S. mutans–C. albicans interactions. This narrative review synthesizes current research on the structural and functional cooperation between these organisms, highlights their combined role in ECC, and discusses emerging therapeutic strategies aimed at disrupting their pathogenic synergy.

Methodology

Search Strategy and Literature Selection

A comprehensive literature search was undertaken to identify relevant studies examining the interactions between *Streptococcus mutans* and *Candida albicans* within the context of dental caries. The search was conducted across four major electronic databases: PubMed, Scopus, Web of Science, and Google Scholar. A combination of MeSH terms and keyword-based queries was used, incorporating the following terms: *"Streptococcus mutans"*, *"Candida albicans"*, *"dual-species biofilm"*, *"cross-kingdom interaction"*, *"dental caries"*, and *"ECC"* (early childhood caries). Boolean operators (AND, OR) were used to refine and expand the search as necessary.

The search was restricted to articles published between January 1986 and April 2024, and limited to studies published in English. Additional sources were identified through manual screening of reference lists from relevant publications.

Eligibility Criteria

Studies were included in the review if they met the following criteria:

- Peer-reviewed publications
- In vitro, in vivo, or clinical studies
- Explicit investigation of *S. mutans–C. albicans* interactions within cariogenic or dual-species biofilms
- Analysis of molecular mechanisms, structural biofilm dynamics, or clinical implications in the context of dental caries

Exclusion criteria comprised:

- Commentaries, or editorials
- Studies investigating single-species biofilms or organisms in isolation
- Articles published in languages other than English
- Studies lacking a clear focus on interkingdom or dual-species interactions

Study Selection and Data Synthesis

Titles and abstracts of retrieved articles were independently screened for relevance. Full texts of potentially eligible studies were then assessed for inclusion based on the outlined criteria. Discrepancies were resolved through consensus. The selected studies were narratively synthesized, with findings organized into thematic categories encompassing: microbial synergy, biofilm structure and virulence, mechanisms of interaction, and therapeutic implications.

Microbial Interactions in Oral Biofilms

Biofilm Architecture and Matrix Enhancement

The formation and stability of oral biofilms are strongly influenced by the structural interplay between bacterial and fungal components. Candida albicans significantly contributes to the architecture of dual-species biofilms by enhancing the activity of Streptococcus mutans glucosyltransferases (Gtfs), particularly GtfB. GtfB is a key enzyme responsible for synthesizing insoluble glucans from dietary sucrose. It binds to the mannoprotein layer on the C. albicans cell wall, catalyzing localized glucan deposition on fungal surfaces [4] This interaction anchors S. mutans cells onto fungal hyphae, facilitating spatial organization and cross-kingdom structural integration.

The resulting extracellular polymeric substance (EPS) matrix is rich in glucans, which serve as scaffolding molecules, embedding both microbial species within a cohesive and protective network. This matrix increases microbial entrapment, supports nutrient retention, and promotes metabolic cooperation, thus enhancing the overall stability and pathogenic potential of the biofilm [5,6] Furthermore, the dense EPS layer acts as a diffusion barrier, limiting the penetration of antimicrobial agents and reducing the impact of environmental stresses such as pH shifts and salivary flow.[3] Consequently, the enhanced architecture contributes to the virulence and persistence of the biofilm in cariogenic conditions. While these findings have been validated in vitro, it remains unclear whether such biofilm architecture persists in vivo under the complexity of host defenses, salivary flow, and dietary fluctuations. Few animal models convincingly replicate this spatial arrangemen.

Environmental and Nutritional Synergy

The ecological success of Streptococcus mutans and Candida albicans in the cariogenic biofilm is heavily influenced by their metabolic cooperation and mutual environmental modulation. C. albicans possesses the enzymatic machinery to ferment a broad range of carbohydrates, leading to the production of ethanol, organic acids (such as pyruvate and acetate), and other acidic byproducts. This metabolic output not only acidifies the microenvironment but also contributes to the demineralization of enamel, supporting the survival and proliferation of aciduric species like S.mutans.[7] The sustained low pH conditions further favor the dominance of these acidogenic organisms, establishing a pathogenic feedback loop.

Conversely, S. mutans metabolizes dietary sucrose to produce lactate, which C. albicans can utilize as a secondary carbon source, enhancing its growth and hyphal transformation. This lactate cross-feeding mechanism reflects a form of metabolic reciprocity that enables both organisms to persist under nutrient-limited and acidic conditions [8,9] Moreover, this cooperation supports robust energy production within the biofilm, leading to increased biomass and virulence. These reciprocal metabolic interactions contribute not only to biofilm maturation and resilience but also to heightened cariogenic potential, particularly in the plaque of individuals with high sugar diets or reduced salivary flow.

Molecular Mechanisms of Interaction

Co-Adhesion via Glucans

A critical aspect of dual-species biofilm formation between Streptococcus mutans and Candida albicans lies in their physical co-adhesion, mediated primarily by glucan-based interactions. S. mutans expresses several glucan-binding proteins (Gbps), notably GbpA and GbpC, which have high affinity for the glucans synthesized by glucosyltransferase enzymes (Gtfs) in the presence of dietary sucrose. These glucans are not only synthesized by S. mutans but can also be formed directly on the surface of C. albicans, particularly through GtfB activity binding to fungal mannans[10]

This molecular tethering enables bacterial cells to attach firmly to the fungal surface, enabling early colonization of enamel and mucosal substrates. The glucan-mediated linkage provides a stable and cooperative framework for the dual-species community, allowing for bacterial microcolonies to anchor onto fungal hyphae or yeast cells.[11] These physical interactions promote spatial organization within the biofilm, leading to a stratified and more resilient structure. The glucan-rich interface not only enhances microbial adhesion but also contributes to biofilm robustness by resisting mechanical shear forces and antimicrobial agents. Thus, glucan-mediated co-adhesion is fundamental in stabilizing bacterial-fungal interactions and is a pivotal step in the pathogenic evolution of cariogenic biofilms.

Transcriptomic Modulation

The synergistic relationship between Streptococcus mutans and Candida albicans in dual-species biofilms is not limited to physical and metabolic interactions; it also involves intricate molecular cross-talk that modulates gene expression in both organisms. Transcriptomic studies reveal that when these species coexist in a biofilm, S. mutans exhibits significant upregulation of key virulence-associated genes. These include gtfB, which encodes a glucosyltransferase responsible for extracellular glucan synthesis; spaP, which contributes to adhesion via antigen I/II; and luxS, a gene involved in quorum sensing and interspecies communication.[12] Simultaneously, C. albicans responds to this microbial interaction by enhancing the expression of hyphal-specific genes such as HWP1 (Hyphal Wall Protein 1) and ALS3 (Agglutinin-Like Sequence 3), which facilitate adhesion and invasion of host tissues. In addition, biofilm regulatory genes such as EFG1 and BCR1 are upregulated, promoting morphological transformation and robust biofilm formation [13] These transcriptional changes are mutually reinforcing, leading to increased virulence, deeper tissue penetration, and greater biofilm resilience.

This bidirectional modulation of gene expression highlights the dynamic adaptability of microbial communities and underscores the importance of targeting interspecies signaling pathways in the development of anti-caries therapies. While transcriptomic shifts such as upregulation of gtfB, luxS, and EFG1 have been well documented in dual-species biofilms, a major limitation is that few studies compare these gene profiles in actual clinical isolates from ECC patients.[13] The reliance on laboratory strains like UA159 and SC5314 may obscure strain-specific interactions. Moreover, emerging evidence suggests epigenetic regulation may play a role in fungal adaptation within bacterial-rich environments—a frontier yet to be explored[24]

Role in Early Childhood Caries (ECC)

Early Childhood Caries (ECC) is a multifactorial disease influenced by microbial, dietary, and host-related factors. Among the microbial contributors, the co-existence of Streptococcus mutans and Candida albicans has emerged as a significant factor in the pathogenesis of ECC. Numerous studies have reported a high prevalence of these two organisms in carious lesions, particularly in cases that are severe, extensive, or recurrent [14,15,16,17]

The synergistic interaction between S. mutans and C. albicans enhances their pathogenic potential. S. mutans is well known for its acidogenic and aciduric properties—it ferments dietary carbohydrates to produce lactic acid, leading to a drop in pH and subsequent enamel demineralization. When C. albicans is present, this effect is amplified. C. albicans not only survives in acidic environments but also provides a scaffold for S. mutans adhesion by contributing to a robust extracellular matrix composed of glucans and mannans. Mechanistically, the interaction is mediated by glucosyltransferase enzymes (Gtfs) secreted by S. mutans, which bind to C. albicans cell walls and facilitate the synthesis of glucans on fungal surfaces. This results in a more cohesive and protective biofilm structure, enhancing the survival of both organisms under hostile environmental conditions such as low pH and limited nutrients.[15]Additionally, this cohabitation increases acid production and prolongs the low pH environment, which accelerates enamel dissolution and lesion progression.

Therapeutic Opportunities and Future Directions

The resilience and virulence of dual-species biofilms formed by Streptococcus mutans and Candida albicans present a significant challenge to conventional caries prevention strategies, such as mechanical plaque removal, fluoride applications, and broad-spectrum antimicrobials. These traditional approaches often fail to disrupt the robust extracellular matrix or address the cooperative metabolic and genetic adaptations of mixed-species communities. Therefore, novel therapeutic interventions are being explored to target the specific mechanisms underpinning bacterial-fungal synergy.

One promising strategy is the use of glucosyltransferase (Gtf) inhibitors**,** such as quaternary ammonium methacrylate derivatives. These compounds interfere with the synthesis of insoluble glucans by S. mutans enzymes (GtfB, GtfC, GtfD), effectively preventing the formation of the extracellular matrix and reducing biofilm cohesion without compromising the mechanical properties of restorative materials.[18]

Targeted antifungal agents**,** including azoles like fluconazole and polyenes such as amphotericin B, are being

investigated for their ability to selectively inhibit C. albicans virulence factors—particularly hyphal development—while preserving beneficial oral microbiota with azoles inhibiting ergosterol synthesis and polyenes binding directly to ergosterol, causing membrane disruption.[9]

While these agents are effective against Candida albicans, resistance mechanisms—particularly with azoles—areemerging**,** including efflux pumps and mutations in the ERG11 gene. The study emphasized the need for

judicious use of antifungals and highlights the importance ofunderstanding resistance pathways to develop new and effective therapies.Additionally, biofilm-disrupting peptides**,** such as analogs of histatin-5 (a salivary peptide with natural antifungal activity), have demonstrated efficacy in disrupting dual-species biofilms. These analogs interfere with fungal adhesion and interkingdom signaling pathways, impairing both C. albicans hyphal morphogenesis and S. mutans co-aggregation mechanisms.[19]

Emerging nanoparticle-based agents, including chitosan and silver nanoparticles, offer potent dual-action antimicrobial effects. Chitosan disrupts microbial adhesion and biofilm structure, while silver nanoparticles generate reactive oxygen species that damage cell membranes and DNA, effectively targeting both bacterial and fungal components of the biofilm.[20] Recent findings also highlight that membrane vesicles released by S. mutans carry active glucosyltransferases capable of enhancing C. albicans biofilm development independently of bacterial cells.[21] Moreover, GtfB from **S.** mutans directly binds to the surface of C.albicans, promoting localized glucan deposition.This interaction strengthens fungal adhesion, enhancing dual-species accumulation and contributing significantly to biofilm virulence.[22]The synergistic interaction between **S.** mutans and **C**. albicans also amplifies biofilm acidogenicity in saliva, driven by their cooperative metabolism of dietary sugars. This metabolic synergy increases the production of organic acids, contributing to enamel demineralization and the progression of dental caries.[23] Intriguingly, S. mutans has also been shown to influence ubiquitin modification pathways within C. albicans, which may alter fungal stress responses and biofilm persistence.[24] Silver-chitosan nanoparticles, which combine the antimicrobial effects of both components, have proven particularly effective in disrupting established dual-species biofilms.[25](Table1)

Table 1. Summary of the key findings

Study	Year	Design	Focus	Key Findings
Loesche et al.	1986	Review	Role of S. mutans	Identified as primary caries pathogen
Bowen & Koo	2011	Review	Glucan matrix biology	Gtf enzymes critical for biofilm virulence
Falsetta et al.	2014	In vivo	Dual-species virulence	Enhanced caries and inflammation
Hwang et al.	2017	In vitro	GtfB–mannan interaction	Promotes co-adhesion with C. albicans
Ellepola et al.	2021	In vitro	GtfB augmentation	Promotes fungal accumulation
Koo et al.	2022	In vivo	Cross-kingdom synergy	Increases enamel demineralization
Zhang et al.	2023	Clinical	ECC co-detection	Dual presence linked to ECC severity
Lee et al.	2024	In vitro	Nanoparticle therapy	Disrupts mature biofilms
Zhou et al.	2020	In vitro	Gtf inhibitors	Reduces EPS and acidogenicity

Natural plant-derived compounds**,** such as purpurin, offer another avenue of intervention by inhibiting C. albicans hyphal formation and downregulating key virulence genes like HWP1 and ALS3[26.] The presence of cariogenic pathogens like S. mutans and C. albicans drastically alters biofilm composition and function, tipping the ecological balance toward disease by enhancing acid production and suppressing beneficial species. [27.] In this context, pH-modulated prebiotics such as xylitol or arginine have shown promise. By selectively supporting beneficial microbial populations and creating unfavorable conditions for S. mutans and C. albicans, they help inhibit dual-species biofilm formation and restore microbial balance. [28]

Clinical studies in early childhood caries (EC**C)** populations have consistently found co-colonization by S. mutans and C. albicans. Their enhanced interaction has been linked to more severe disease manifestations, underscoring the need for therapeutic strategies that address both organisms simultaneously.[29] Finally, CRISPR-Cas technologies have emerged as a precision-based therapeutic option. Targeting virulence genes in S. mutans, such as gtfB, spaP, and comDE, has been shown to reduce biofilm formation and cariogenicity, offering a novel and highly specific tool for microbial control without disrupting commensal flora[30](Table2)

Table 2.Theuraptic implications of synergism on dental caries

Author(s)	Year	Title	Study Type	Key Findings
Zhou Y et al.	2020	Antibiofilm efficacy of a quaternary ammonium methacrylate in combination with fluoride	In vitro	Gtf inhibitors reduce biofilm formation in dual-species (S. mutans + C. albicans) biofilms
Ellepola K et al.	2021	GtfB augments Candida albicans accumulation in biofilms	In vitro	GtfB from S. mutans binds to mannans of C. albicans, enhancing co-adhesion
Koo H et al.	2022	Cross-kingdom biofilm synergism in a mouse model	In vivo (animal)	Dual-species biofilms cause more severe enamel damage and inflammation
Zhang L et al.	2023	Prevalence of S. mutans and C. albicans in ECC lesions	Clinical	Co-detection significantly higher in children with ECC than healthy controls
Lee J et al.	2024	Silver-chitosan nanoparticles disrupt oral biofilms	In vitro	Nanoparticles effective against bacterial-fungal biofilms
Tsang PW et al.	2021	Purpurin suppresses Candida albicans virulence	In vitro	Reduced hyphal formation and biofilm when co-cultured with S. mutans
Liu Y et al.	2021	Quorum sensing interference in dual-species biofilms	Transcriptomics	Disruption of LuxS signaling pathway reduces biofilm resilience
Silva MJ et al.	2022	Effect of pH-modulated prebiotics on ECC biofilms	In vitro	Prebiotics targeting pH balance altered microbial ratios
Costa L et al.	2023	Fungal–bacterial interactions in ECC plaque samples	Clinical	Dense glucan–mannan matrix associated with severe ECC cases
Wang R et al.	2024	CRISPR-Cas targeting of S. mutans virulence genes	In vitro	CRISPR knockouts of gtfB and luxS reduced co-biofilm virulence

CONCLUSION

The synergistic interactions between Streptococcus mutans and Candida albicans have emerged as a critical factor in the development and persistence of cariogenic biofilms. A growing body of in vitro and in vivo evidence indicates that co-adhesion mechanisms, glucosyltransferase-mediated matrix enhancement, and metabolic cooperation between these species contribute to increased biofilm maturation, acidogenicity, and resistance to conventional therapeutic strategies. These findings are particularly relevant in the context of early childhood caries and among immunocompromised individuals, where dual-species biofilms appear to be more prevalent and resilient.

Nevertheless, while the current data strongly support a synergistic model of pathogenesis, it is important to recognize the limitations and variability across studies. Some clinical investigations demonstrate mere co-colonization without definitive evidence of exacerbated cariogenicity, suggesting that host factors, ecological conditions, and inter-microbial competition within the oral microbiome may influence the extent and impact of these interactions. Furthermore, the heterogeneity in experimental models—ranging from salivary constituents to substrate type and pH—warrants cautious extrapolation of in vitro results to the clinical setting.

Therefore, while dual-species biofilms represent a promising target for novel anti-caries interventions—such as glucosyltransferase inhibitors, biofilm-disrupting peptides, nanoparticle-based agents, and CRISPR-mediated gene targeting—further clinical and mechanistic studies are essential to validate these strategies. A deeper understanding of the dynamic interplay between S. mutans, C. albicans, and the host environment will be pivotal in translating these findings into effective, patient-specific therapeutic approaches.

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The authors have no competing interests to declare.
Ethical Approval
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Informed Consent
Not applicable.

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