Review



# Oral Mycobiome: Composition, Functionality and Clinical Implication

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*Review*

# Oral Mycobiome: Composition, Functionality and Clinical Implication

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**Abstract**

Historically, the study of oral fungal species was limited by the inability to cultivate most of them. However, advances in metagenomic techniques have enabled the direct identification of microbial genomes from human samples, markedly broadening our understanding of the oral mycobiome. This literature review aims to analyze the available scientific evidence on the composition and dynamics of the oral mycobiome, as well as its influence on the development of local pathological conditions. The oral mycobiome is highly diverse, with emphasis on genus *Candida,* followed by *Malassezia, Aspergillus, Saccharomyces, Cladosporium*, *Trichosporon* and *Geotrichum*. *Candida albicans* remains the most frequently identified species in both health and diseases state. However, individuals with oral candidiasis present a higher detection of *Candida dubliniensis*, *Candida parapsilosis*, *Pichia kudriavzevii, Antrodiella micra* and *Cladosporium sphaerospermum*. In dental caries, *C. albicans* and *C. dubliniensis* are associated with advanced lesions, whereas *Malassezia* and *Rhodotorula* may exert protective effects against cariogenic bacteria. In periodontitis, an increase in yeast-bacteria interactions is observed. Additionally, *C. albicans* has been implicated in oral carcinogenesis through multiple mechanisms. These findings highlight the need for a deeper understanding of the oral mycobiome to enable early detection of oral diseases and the development of therapeutic approaches.

**Keywords:** dysbiosis; human microbiome; mycobiome; microbiota; oral cavity; oral fungal microbiome

## 1. Introduction

The oral cavity hosts a high quantity of microorganisms, second only to the gastrointestinal tract. This oral microbial community is diverse and includes bacteria, fungi, viruses and archaea, which coexist in dynamic equilibrium and play important roles in maintaining oral and systemic health [1,2]. However, microbe-host interactions can be constantly affected by lifestyle habits and environmental factors, causing changes in the microbial groups that normally predominate, leading to an imbalance that favors the emergence of diseases, a condition known as dysbiosis [3].

Many of these microorganisms cannot be easily cultivated in the laboratory, which has historically limited their study. With the advancement of metagenomic techniques, it has become possible to identify complete genomes directly from human genetic material, without the need for prior cultivation. Nowadays, it is possible to identify both bacterial and fungal taxa in human samples by amplifying and sequencing specific genes. For bacteria, the 16S ribosomal RNA gene is commonly used, while fungi are analyzed by sequencing the 18S ribosomal RNA and the internal transcribed spacer (ITS) region [9].

This progress has significantly expanded our understanding of the composition of oral microbiomes, as well as their essential role in health and diseases status [1]. Most studies related to oral microbiome have focused on bacteria (bacteriome); however, many other microorganisms may

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be present in the oral cavity, including a variety of fungal species (mycobiome). The oral mycobiome corresponds to less than 0.06% of the microorganisms in saliva and only 0.0001% in dental plaque [5].

Although fungi represent a smaller part of the microbiome compared to bacteria, they can play an important role in homeostasis and dysbiosis, contributing to the health or damage of oral mucosal tissues. Therefore, it is essential to recognize the presence and influence of the fungal component in the maintenance of oral health, which can help us identify possible relationships between fungal dysbiosis and oral diseases [4]. Certain fungal species are naturally part of the human microbiome, but many fungi can be acquired from the environment and just pass through the oral cavity. Some even fail to develop in the oral cavity because of unfavorable conditions, such as temperature or competition for nutrients with bacteria. It is therefore essential to know which fungi can multiply in the mouth, to avoid misinterpretation of mycobiome data.

In addition, the low abundance and limited sensitivity of some detection techniques raise doubts as to whether these fungi are only passingly present or whether they are in fact commensals or possible disease-causes [6]. Consequently, there is still a paucity of data on the mycobiome, especially when compared to the knowledge available on bacteria [8]. This literature review aims to analyze the available scientific evidence on the composition, dynamics and functionality of the oral mycobiome, providing an understanding about the main factors that modulate the fungal balance in the oral cavity and the mechanisms by which dysbiosis contributes to the development of local pathological conditions.

## 2. Healthy Oral Mycobiome

There are several studies dedicated to characterizing commensal mycobiome in healthy individuals. In these studies, the terms “central mycobiome” or “basal mycobiome” is commonly used to refer to the components of the mycobiome that remain relatively stable over time in these individuals [9,11,13].

To understand the role of the mycobiome in oral diseases, it is essential to first know its composition under healthy conditions. One of the first studies to analyze the oral mycobiome employed oral buccal samples from healthy individuals of different ethnicities with a Western diet. In total, it was found 74 culturable and 11 non-culturable fungal genera from the oral cavity of studied population. This study also revealed between 9 and 23 cultivable species per individual. From this, a set of genera associated with the basal oral mycobiome was defined, including *Alternaria, Aspergillus, Aureobasidium, Candida, Cladosporium, Cryptococcus, Dothioraceae, Eurotium, Fusarium, Glomus, Saccharomyces, Saccharomycetales* and *Teratosphaeria* [14].

Using genome sequencing techniques, later studies also identified *Malassezia, Irpex, Cytospora/Valsa, Lenzites/Trametes* and *Sporobolomyces/Sporidiobolus* as possible members of the healthy mycobiome [11,12]. Based in these studies, it is known that the basal oral mycobiome is predominantly composed of *Candida* (40–70%), followed by *Cladosporium* (2–20%), *Aureobasidium* (4–6%) and fungi from the Saccharomycetales order (13%). *Aspergillus* (2%), *Fusarium* (1–3%) and *Cryptococcus* (0.5–2%) occur in less abundance [14]. The fungal genera found in the oral cavity tend to dominate individual samples in a mutually exclusive manner, forming distinct fungal communities known as mycotypes. Recent evidence indicates that these mycotypes are associated with specific clinical characteristics as well as corresponding bacterial profiles [7,13]. The least diverse mycotype, dominated by *Candida*, was related to an equally less diverse bacteriome, with a predominance of acidogenic and aciduric bacteria, such as *Lactobacillus* and *Propionibacterium*.

On the other hand, more diverse communities dominated by *Malassezia* were associated with a more complex bacteriome, enriched with inflammatory species from the genera *Fusobacterium, Porphyromonas, Prevotella* and *Leptotrichia*, among others. In addition, the mycotypes are correlated with specific clinical characteristics. For example, *Candida* dominated communities were more frequent in smokers, dental prostheses users, and individuals that take corticosteroids, possess a higher plaque index and/or have active caries [13]. Therefore, in this review, we discuss specific

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factors that modify the oral mycobiome and lead to dysbiosis, which consequently can result in diseases, such as oral candidiasis, dental caries, periodontal diseases and dysplasia.

## 3. Factors that Modify Oral Mycobiome

In the oral health condition, the microorganisms that compose the microbiome maintain a beneficial and balanced relationship, acting together to prevent the colonization and establishment of pathogens in the oral cavity [15]. In general, the fungi present in the microbiome remains in a commensal state, being harmless or even performing defense functions. When this microbial community is suppressed or eliminated, fungal organisms can become prominent, favoring the proliferation of pathogenic microorganisms and triggering inappropriate inflammatory or immune responses against commensal microorganisms [17].

In this context, various intrinsic and extrinsic host factors can modulate the composition and balance of the oral mycobiome, favoring both the maintenance of homeostasis and the establishment of a dysbiosis state [18]. Intrinsic factors are mainly related to the individual's immune status. Age is also a relevant factor: in the elderly, there is a tendency towards a reduction in the diversity of the mycobiome and greater susceptibility to oral candidiasis, possibly due to changes in salivary production and the innate immune response. In addition, genetic and hormonal characteristics can modulate the composition of the mycobiome, as evidenced by fungal alterations associated with hormonal variations during pregnancy [19]. Among extrinsic factors, the use of medication, especially antibiotics and antifungals, can cause significant imbalances in the oral mycobiome. Prolonged use of antibiotics reduces bacterial competition, favoring the growth of fungi, mainly of the *Candida* genus. In addition, smoking and alcohol consumption are among the main behavioral factors that negatively affect oral mycobiome [19].

In relation to intrinsic factors, patients with genetic immunological disorders generally present alterations in the oral mycobiome. Patients with defects in the Th17/IL-17 axis, present recurrent oral fungal infections. Analysis of fungal communities in the oral mucosa of these patients revealed severe dysbiosis with *Candida albicans* dominance. Active candidiasis was associated with decreased microbial diversity and enrichment of *Streptococcus oralis* and *Streptococcus mutans*, suggesting a cross-kingdom interaction of *C. albicans* with oral *streptococci* [15,39].

Human immunodeficiency virus (HIV) infection has also a substantial impact on the composition and balance of the oral microbiome, primarily due to immunosuppression caused by the progressive reduction in $CD4^+$ T cells [25]. Studies showed that people living with HIV (PLHIV) have a significant increase in colonization by opportunistic fungi, especially species of the *Candida* genus, particularly *Candida albicans*. Other species such as *Nakaseomyces glabratus* (formerly known as *Candida glabrata*), *Candida tropicalis*, *Pichia kudriavzevii* (formerly known as *Candida krusei*), and *Candida dubliniensis* are also frequently detected in this group, especially in patients with CD4 counts below 200 cells/$mm^3$ [24,25]. In addition to the increased fungal load, there is a reduction in the diversity of the oral mycobiome, characterized by the predominance of a few taxa and a decrease in the presence of commensal fungi that, under normal conditions, contribute to the oral ecological balance [25].

Another relevant aspect in PLHIV is the intensification of interactions between fungi and pathogenic bacteria. *C. albicans* can interact with *S. mutans, Porphyromonas gingivalis*, and other oral microorganisms, forming complex and resistant biofilms that hinder the action of the immune system and antimicrobial agents. These microbial interactions contribute to the persistence of infection and the worsening of oral manifestations [26].

Clinically, these changes in the oral mycobiome translate into a higher incidence of fungal infections, particularly oral candidiasis in its various clinical forms, which remain common manifestations of HIV infection, even after the advent of antiretroviral therapy (ART) [26]. ART, in turn, can contribute to partial recovery of the immune system and a reduction in oral fungal load. However, complete normalization of the oral mycobiome is not always achieved, and the effect of ART on fungal composition can vary depending on the therapeutic regimen, treatment adherence, and the patient's immune status [30]. Therefore, HIV is directly associated with oral mycobiome

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dysbiosis, characterized by reduced fungal diversity, increased colonization by opportunistic species, and a favored pathogenic interaction. These changes not only reflect systemic immunosuppression but can also contribute to local complications, chronic inflammation, and an increased risk of potentially malignant lesions in the oral mucosa [30].

In the context of extrinsic factors, Sajid et al. [21] conducted a pilot study to evaluate the impact of smokeless tobacco consumption on the oral mycobiome by sequencing the fungal ITS1 region from oral swab samples. By comparing non-users of smokeless tobacco with users presenting or not oral candidiasis lesions, the authors demonstrated that chronic smokeless tobacco exposure is associated with significant oral mycobiome dysbiosis, characterized by a marked reduction in overall fungal load and diversity. These alterations were particularly pronounced in individuals with oral lesions, suggesting a link between tobacco-associated mycobiome disruption and oral mucosal pathology.

In a complementary investigation, Sajid et al. [22] focused on the composition and ecological functionality of fungal communities associated with smokeless tobacco products predominantly consumed in India. This study provided a more detailed ecological perspective, showing that non-users exhibited a healthier oral mycobiome profile, with higher fungal diversity and a predominance of *Candida* species accounting for approximately 40–70% of the community. In contrast, tobacco users—especially those with oral lesions—displayed reduced richness and diversity, along with an increased relative abundance of non-*Candida* genera such as *Pichia* (~10–15%). Importantly, the combined use of smokeless tobacco and alcohol further exacerbated these compositional shifts, resulting in the most pronounced fungal imbalance. Collectively, these findings support the hypothesis that sustained exposure to smokeless tobacco promotes oral mycobiome dysbiosis, which may contribute to oral carcinogenesis through disruption of fungal ecological homeostasis [21,22].

In addition, various studies showed that chronic alcohol use has significant effects on the oral mycobiome, promoting changes in its composition, diversity, and ecological balance. Ethanol, the main component of alcohol, and its metabolite acetaldehyde contribute to this imbalance by promoting changes in oral pH, mucosal damage, and impaired local immunity [30]. This environment favors the proliferation of opportunistic fungi, especially *C. albicans, N. glabrata*, and *C. tropicalis*. The increased presence of these fungi is related to increased adhesion to the oral mucosa, a greater capacity to form biofilms, and increased expression of virulent genes [31]. The fungal growth also leads to the formation of complex oral biofilms, often involving synergistic interactions between *Candida* and pathogenic bacteria, such as *S. mutans*. Such biofilms are more resistant to the host immune response and antimicrobial treatments [32].

Thus, scientific evidence indicates that the oral mycobiome is strongly influenced by a combination of intrinsic and extrinsic factors. Understanding of these influences is fundamental not only for the prevention of oral fungal infections, but also for the development of therapeutic strategies that aim to restore and maintain oral fungal balance in different clinical and population contexts. In this scenario, many researchers have sought to identify the oral mycobiome profile under specific conditions of oral cavity, particularly in the presence of candidiasis lesions, dental caries, periodontal diseases and dysplasia or cancer (Table 1).

**Table 1.** Fungal species identified in the oral cavity according to clinical condition and molecular identification methods.

| Main microorganisms identified | Clinical sample/Health/Disease | Form of molecular analysis and identification | Country/Reference | Reference |
|---|---|---|---|---|
| *Candida albicans*, *Rhodotorula slooffiae*, *Debaryomyces hansenii*, *Geotrichum candium*, *Toxicocladosporium irritans* | Mouth rinse, tongue scraping from patients with pseudomembranous oral candidiasis and healthy controls | LH-PCR | Japan | [75] |
| *Candida albicans*, *Candida dubliniensis*, *Candida tropicalis*, *Trichosporon cutaneum*, *Exophiala equina* | Mouth rinse from patients with pseudomembranous oral candidiasis and healthy controls | NGS | Japan | [73] |
| *Candida albicans*, *Pichia kudriavzevii*, *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis* | Oral biopsy tissue from non-smoker patients with dysplasia, oral squamous cell carcinoma, and histologically benign lesions | PCR-RFLP | Turkiye | [62] |
| *Candida albicans*, *Mallassezia globosa*, *Mallassezia restricta*, *Aspergillus penicillioides*, *Cladosporium exasperatum* | Tissue sample from patients with oral squamous-cell carcinoma | qPCR | Sri Lanka | [54] |
| *Candida*, *Ascomycota*, *Phoma*, *Trichosporon*, *Penicillium*, *Aspergillus e Coniochaeta* | Saliva from patients with oral lichen planus | NGS | China | [52] |
| *Pichia kudriavzevii*, *C. tropicalis* , *Pichia anômala*, *C. famata* , *C. glabrata*, *C. rugosa*, *C. orthopsilosis*, *C. kefyr*, *C. lusitaniae*, and *C. stellatoides* | Saliva from patients with oral squamous cell carcinoma, oral potentially malignant disorders and healthy cohorts. | PCR-RFLP | India | [63] |

| | | | | |
|---|---|---|---|---|
| *C. albicans, C. dublinienses, C. parapsilosis. e Aspergillus niger.* | Mouth rinse from patients with periodontal disease and good oral health | NGS | USA | [47] |
| *Rigidoporus vinctus, Candida parapsilosis, Candida albicans, Candida dubliniensis, Saccharomyces cerevisiae Trametes elegans.* | Saliva from patients with periodontal disease | NGS | Puerto Rico | [48] |
| *Candida albicans, Candida dubliniensis, Neoscytalidium oryzae* | Supragingival plaque samples obtained from children with different caries status. | NSG | USA | [34] |

Caption: Length Heterogeneity Polymerase Chain Reaction (LH-PCR), Next-Generation Sequencing (NGS), Polymerase Chain Reaction – Restriction Fragment Length Polymorphism (PCR-RFLP).

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## 4. The Relationship Between Mycobiome and Oral Diseases

### *4.1. Mycobiome and Oral Candidiasis*

Oral candidiasis is the most common fungal infection, frequently occurring in individuals weakened by other diseases or clinical conditions, and is therefore commonly classified as an opportunistic disease [10,14,74]. It is predominantly caused by *C. albicans*; however, the widespread use of antifungals, both empirically and prophylactically, in recent years has contributed to a change in this scenario, favoring the emergence of other yeast species, including non-*C. albicans* species such as *N. glabratus, C. tropicalis, P. kudriavzevii*, and *C. dubliniensis*. Due to the change in the infection profile of candidiasis, it becomes necessary to improve rapid techniques for the accurate identification of species and study of the mycobiome, thus enabling correct treatment and the choice of appropriate antifungal therapy in the face of fungal infections [71,73].

Ieda et al. [78] investigated the mycobiome of patients with oral candidiasis and evaluated changes following antifungal therapy using PCR analysis combined with ITS length heterogeneity profiling. The study included 52 patients with pseudomembranous oral candidiasis and 30 healthy individuals as controls. Affected patients exhibited greater fungal species diversity and a higher fungal burden compared to controls. *C. albicans* was the most frequently identified species in both groups; however, *C. dubliniensis* was detected at a significantly higher proportion in patients with pseudomembranous oral candidiasis. Considering only LH-PCR peaks with an area ≥1% of the total, the study reported fungi such as *C. albicans, Rhodotorula slooffiae, Debaryomyces hansenii, Geotrichum candidum, Toxicocladosporium irritans, Ceriporia lacerata, Malassezia restricta, C. dubliniensis*, and *Rhodotorula minuta*, among others. After antifungal treatment, a marked reduction in the detection of *C. dubliniensis* was observed, and the mycological profile of patients with candidiasis became similar to that of the control group. There was a significant decrease in the total and mean number of detection signals per individual. Additionally, the detection rate of *C. albicans* increased, whereas *C. dubliniensis* became virtually undetectable [78].

Imabayashi et al. [73] investigated the oral fungal biodiversity of patients with oral candidiasis and healthy individuals, in which fungal populations were quantified using real-time PCR targeting the ITS region, and species diversity was further assessed through NGS analysis of the ITS1 region in both groups. A total of 107 fungal species were identified, with the total and mean number of species per individual being higher in the control group than in patients with oral candidiasis. *C. albicans* accounted for more than 80% of the total fungal population in both groups, and the proportion of *C. dubliniensis* was higher in patients with oral candidiasis compared to healthy individuals. In relation to other fungal species, *C. parapsilosis, Wallemia sebi, Rhodosporidium babjevae, P. kudriavzevii, Antrodiella micra, Cladosporium sphaerospermum*, and species belonging to the order *Sporidiobolales* were detected at significantly higher rates in patients with oral candidiasis. Conversely, *Exophiala equina*, *Cladosporium halotolerans*, and species of *Agaricomycetes* were more frequently detected in controls [73]. Notably, some species identified in this study, including *Exophiala equina, Meyerozyma guilliermondii*, and *Trichosporon cutaneum*, had not previously been reported as part of the oral mycobiome, likely due to limitations of earlier detection techniques. Given that *Meyerozyma guilliermondii* and *Trichosporon cutaneum* have been associated with systemic mycoses, these findings suggest that oral candidiasis may potentially contribute to the pathogenesis of systemic fungal infections [73].

Lin et al. [77] analyzed the salivary mycobiome of individuals living with HIV/AIDS at different stages of infection, including some patients with oral candidiasis, and compared these profiles with those of HIV-negative controls. Using next-generation sequencing (ITS region), the authors observed that mycobiome diversity in HIV-positive individuals decreased progressively as the disease advanced. The lowest level of diversity was identified in patients at HIV stage 3, corresponding to the most advanced phase of infection (AIDS). Additionally, it was observed a transient increase during the early stage of infection (HIV stage 0) compared with HIV-negative controls, followed by a gradual decline as the infection progressed. These findings suggest that salivary mycobiome

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analysis may serve as a potential non-invasive biomarker for monitoring HIV progression and may also support the development of future diagnostic and preventive strategies targeting oral fungal infections [77].

Lin et al. [77] also emphasized the dynamic changes in the salivary mycobiome throughout the progression of HIV infection. Regarding taxonomic composition, it was observed that at the phylum level, all groups were predominantly composed of Ascomycota, followed by Basidiomycota. At the genus level, *Alternaria* and *Talaromyces* showed low abundance in the control group but increased following HIV infection, suggesting that these genera may be present at different stages of the disease. In contrast, *Coniosporium* and *Sarcinomyces* exhibited reduced abundance after infection. Additionally, *Debaryomyces* and *Talaromyces* demonstrated a moderate positive correlation with $CD4^+$ T-cell counts, whereas *Penicillium* showed a negative correlation with viral load. There were no significant differences in mycobiome composition between individuals living with HIV/AIDS with and without candidiasis. These findings indicate that certain oral fungal populations in HIV-infected individuals may be influenced by both $CD4^+$ T-cell counts and viral load levels [77].

These findings suggest that mycobiome characterization enables understanding of fungal populations dynamic in health and disease, indicating that a marked increase in a particular species, accompanied by a relative decrease in others, may promote the development of oral candidiasis [16,79].

### *4.2. Mycobiome and Dental Caries*

Dental caries is a multifactorial disease characterized by the demineralization of hard dental tissues resulting from acids produced by the fermentation of dietary carbohydrates by oral microorganisms present in the dental biofilm [23,29]. The role of dental biofilm bacteria in the etiology of caries is well established, and over the past two decades, the application of molecular techniques has demonstrated the high diversity of oral bacteria communities, as well as their association with disease development [34,41].

Since advances in molecular techniques have significantly expanded the list of microorganisms potentially involved in the pathogenesis of caries, the role of the oral mycobiome in dental caries has attracted increasing scientific interest. Several studies have investigated the diversity of the fungal community in relation to the presence or absence of caries, revealing significant differences in mycobiome composition according to the host's oral health status [4,34].

O'Connell et al. [34] aimed to clarify the complex microbial interactions involved in the etiology and progression of early childhood caries. Using ITS region sequencing, they generated taxonomic profiles from supragingival plaque samples collected from children under different clinical conditions: (1) caries-free, (2) with active caries confined to enamel, (3) with active caries involving dentin. A total of 139 fungal species were identified, with *C. albicans* being the most abundant, followed by *C. dubliniensis*. The researchers found significant differences between the supragingival plaque mycobiome of caries-free children and that of children with lesions extending into dentin. Species such as *C. albicans, C. dubliniensis, Neoscytalidium oryzae*, and unclassified species of the genus *Microdochium* were associated with caries, whereas 12 other taxa were linked to oral health. Notably, *C. dubliniensis* showed a progressive increase as caries advanced into dentin. In contrast, four fungal genera associated with oral health, *Debaryomyces, Rhodotorula, Aureobasidium*, and *Aspergillus*, demonstrated potential antagonistic activity against *Streptococcus mutans*, a key cariogenic bacterium [34].

In the study conducted by Jesus et al. [38], the oral mycobiome of 40 children with caries and 40 caries-free children was compared using next-generation sequencing (NGS) of the ITS1 region of rRNA. The results demonstrated relevant differences in the variety of species present within each group. The genus *Candida* was the most abundant, being detected in 68 of the 73 samples, with higher prevalence in the caries group. At the species level, *C. dubliniensis* was the dominant species among affected children, whereas no significant difference in the abundance of *C. albicans* was observed between children with and without caries. Additionally, species belonging to the genera

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*Mycosphaerella, Cyberlindnera*, and *Trichosporon* showed differences in abundance when comparing caries-free and caries-affected groups [38].

Fechney et al. [33] evaluated the composition of the oral mycobiome using next-generation sequencing (NGS) of the ITS2 region, amplified from dental plaque samples collected from 17 children. In total, 23 genera and 46 fungal species were detected across all plaque samples, with *C. albicans, Naganishia diffluens, Rhodotorula mucilaginosa*, and *Malassezia globosa* being the most abundant species. Although the overall diversity of fungi was similar regardless of the presence of caries, the disease was found to be associated with changes in the abundance of specific fungal species, corroborating other studies [27,33].

Tu et al. [46] used V3–V4 16S rRNA and ITS1 rRNA gene amplicon sequencing to analyze salivary bacterial and fungal profiles in children with and without caries. In both groups, *Candida* was the most abundant fungal genus, followed by *Cladosporium, Aspergillus, Wallemia*, and *Malassezia*. A significant alteration in the salivary fungal community was observed in children with caries compared to the caries-free control group, and the fungal type influenced the structure of the bacterial community. As for health-related taxa, fungal genus *Leptospora* was positively associated with the bacterial genus *Streptococcus*, while it was negative correlated with genus *Prevotella.* Regarding caries-related taxa, *Hannaella, Vishniacozyma* and *Lepista* were found to be positively associated with the bacterial genera *Actinomyces* or *Bergeyella* [46].

Du et al. [44] investigated the role of *C. albicans* in the etiology of dental caries from an ecological perspective. Through in vitro and in vivo experimental models, the study showed that the presence of *C. albicans* significantly altered the composition of the bacterial community within the biofilm, favoring acidogenic and aciduric microorganisms associated with enamel demineralization. The interaction between the fungus and cariogenic bacteria enhanced the formation of more structured and metabolically active biofilms with greater acid-producing capacity. Moreover, colonization by *C. albicans* was associated with increased severity of carious lesions. These findings indicate that *C. albicans* is not merely an opportunistic colonizer, but an ecological modulator capable of reshaping the oral microbiota toward a dysbiotic state, thereby increasing the cariogenic potential of the biofilm. The study reinforces the concept of dental caries as a polymicrobial disease and highlights the importance of considering the oral mycobiome in understanding its pathogenesis and in the development of preventive and therapeutic strategies [44].

In summary, there is clear evidence that the mycobiome plays a role in the development of carious lesions, particularly in the more advanced stages of the disease. However, further studies are needed to better understand how fungi interact with oral bacteria and how these interactions may enhance the virulence of the polymicrobial oral biofilm in dental caries [38,46].

### *4.3. Mycobiome and Periodontal Diseases*

Periodontitis is a chronic inflammatory disease that affects the periodontium, the tissues responsible for surrounding and supporting the teeth. It is highly prevalent among adults and represents the leading cause of tooth loss worldwide. Its etiology is associated with a synergistic and dysbiotic microbial community present in the subgingival biofilm, in which keystone pathogens play a central role in disrupting tissue homeostasis. In addition to bacteria, fungi may also be an important component of the subgingival biofilm. The combined action of these microorganisms, organized within polymicrobial communities, influences the clinical progression of the infection and may impact therapeutic strategies. Therefore, a deeper understanding of the involvement of the mycobiome in periodontitis is essential to improve treatment approaches, especially considering that most studies have predominantly focused on the bacteriome [47,49,51,58].

The oral mycobiome of individuals with and without periodontal disease was characterized using NGS of the ITS region in the study conducted by Peters et al. [47]. Across all analyzed samples, at least four phyla, Ascomycota, Basidiomycota, Glomeromycota and Chytridiomycota were identified, as well as a minimum of 81 genera and 154 fungal species. *Candida* and *Aspergillus* were the most frequently detected genera, being isolated in 100% of the participants, followed by

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*Penicillium* (97%), *Schizophyllum* (93%), *Rhodotorula* (90%), and *Gibberella* (83%). At the species level, three taxa were observed in all individuals: uncultured Dikarya, *Candida* spp., and *Aspergillus niger*. Among these, *Aspergillus niger* and *Candida* spp. were the most abundant species in the samples. *Candida* genus showed higher relative abundance in participants with periodontal disease compared to periodontally healthy individuals, although this difference was not statistically significant. This study was the first to characterize the oral mycobiome in relation to periodontal disease using a comprehensive targeted sequencing approach [47].

The diversity of the mycobiome was assessed among individuals without periodontitis, with mild periodontitis, and with moderate to severe periodontitis in the study conducted by Acosta-Pagán et al. [48]. The most abundant genera across all categories included *Candida, Saccharomyces, Rigidoporus, Aspergillus*, and *Trametes,* with *Aspergillus* being among the most representative. Species-level characterization of the mycobiome was performed comparing healthy participants and those with periodontal disease. The healthy mycobiome was predominantly composed of *Rigidoporus vinctus, C. parapsilosis*, and *C. albicans*, while species such as *C. dubliniensis, Saccharomyces cerevisiae*, and *Trametes elegans* were detected at lower levels. In contrast, participants presenting any degree of periodontal disease exhibited a higher relative abundance of *C. tropicalis, Saccharomyces cerevisiae, Rigidoporus vinctus*, and *Irpex lactus* [48].

Yao Hu et al. [53] conducted a narrative review exploring the role of fungi in periodontitis, particularly species of the genus *Candida.* The review analyzed clinical articles, observational studies, and trials addressing the presence and impact of *Candida* in periodontal tissues. The review shows that several *Candida* species are frequently detected in the oral cavity of individuals with periodontitis and suggests that these yeasts may not merely be opportunistic colonizers, but may also act as co-factors in the inflammatory process. The species most commonly cited in the literature include *C. albicans,* which is the most prevalent and most extensively studied in this context. In addition, other non-*albicans Candida* species have also been reported in association with periodontitis, such as *N. glabratus, C. tropicalis, and C. parapsilosis*. These species vary in their virulence and biofilm-forming capacity, and may interact with periodontopathogenic bacteria, thereby influencing the periodontal pocket microenvironment. In addition, the review discusses potential mechanisms by which *Candida* may contribute to inflammation and tissue destruction, including the formation of mixed biofilms with bacteria, the induction of dysregulated immune responses, and the production of fungal metabolites that may amplify periodontal inflammation. The authors also suggest that, given the growing evidence of fungal involvement in periodontitis, *Candida* species could represent therapeutic targets in ecological management strategies for the disease [53].

Based on the literature surveyed, the main fungal genera isolated from the oral microbiome of individuals with periodontitis appears to coincide with those present in the central mycobiome. However, the precise role of fungi in the onset and progression of periodontitis has yet to be fully elucidated [50].

## 5. Microbiome and Alterations of the Oral Mucosa

In recent years, growing scientific attention has been directed toward understanding the role of the oral mycobiome in the development of oral mucosal alterations, and dysbiotic fungal communities have been consistently identified in these conditions. Among the most common alterations associated with changes in the oral mycobiome are leukoplakia, dysplasia, and carcinoma. Increasing evidence suggests that microbial dysbiosis is not merely a consequence of the tissue changes linked to these lesions, but may precede their onset and actively contribute to their development and progression [55,57,59].

A deeper understanding of microbial dysbiosis concepts, together with advances in high-throughput molecular sequencing technologies, has enabled a more detailed microbiological characterization of clinical conditions, highlighting the association between fungal presence and oral mucosal alterations [60]. In this context, several clinical studies have sought to investigate and characterize the fungal communities associated with various oral mucosal alterations.

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In this context, Li et al. [52] focused on oral lichen planus (OLP), a chronic inflammatory condition of the oral mucosa that affects approximately 0.5% to 2% of the adult population. Their study was conducted in individuals with reticular OLP (n = 17) and erosive OLP (n = 18), that were compared to healthy controls (n = 18). [52]

The oral mycobiome was analyzed using NGS of the ITS2 region. Fungal community composition was assessed at different taxonomic levels. At the phylum level, significant differences were observed between the two predominant phyla: Ascomycota (59.03% in healthy controls, 69.58% in reticular OLP, and 68.22% in erosive OLP) and Basidiomycota (15.62%, 13.46%, and 7.33%, respectively). [52]

At the genus level, a total of 280 genera were detected. The relative abundance of *Candida* and *Aspergillus* was significantly increased in the reticular OLP group compared to healthy controls. In contrast, the genus *Trichosporon* were notably more abundant in healthy individuals than in those with erosive OLP. Overall, the oral fungal community exhibited reduced enrichment and lower complexity in OLP patients compared to healthy individuals. The authors concluded that the oral cavities of OLP patients harbor a dysbiotic and less complex mycobiome, suggesting that fungal dysbiosis is associated with disease progression and severity [52].

The oral mycobiome associated with oral squamous cell carcinoma have also been investigated through quantification of the internal transcribed spacer 2 (ITS2). Perera et al. [54] analyzed oral samples from 25 individuals with carcinoma and 27 controls. A total of 364 species belonging to 162 genera and two phyla were identified. The phyla Ascomycota and Basidiomycota accounted for 78.4% and 21.6% of the mycobiome, respectively. At the genus level, *Candida* was detected in 100% of the samples and represented 48% of the average mycobiome composition. The genera *Malassezia, Cladosporium,* and *Aspergillus* were identified in at least 75% of the samples, with mean relative abundances of 11%, 6.1%, and 3.7%, respectively. [54]

At the species level, *C. albicans* was present in all samples, with a mean relative abundance of 44.4%. *Malassezia restricta, Aspergillus penicillioides*, and *Malassezia globosa* were detected in 83%, 70.2%, and 68.1% of samples, corresponding to 3.2%, 2.2%, and 4.2% of the average mycobiome, respectively. Control samples showed significantly greater species richness and alpha diversity compared to the carcinoma group. *C. albicans, C. etchellii,* and a potentially novel species related to *Hannaella luteola* were significantly enriched in the carcinoma group. Although *C. albicans* was detected in 100% of samples, its mean relative abundance in carcinoma cases was twice that observed in controls. The *H. luteola*-like species was detected in 20% of carcinoma samples and was absent in controls [54].

The prevalence of *Candida* species in the saliva of patients with oral squamous cell carcinoma, with potentially malignant oral lesions, and healthy individuals was evaluated using the PCR-RFLP method by Sankari et al. [63]. The findings revealed a predominance of non-albicans *Candida* species across all three groups. In the oral squamous cell carcinoma group, the non-albicans species identified were: *P. kudriavzevii* (21%), *C. tropicalis* (21%), *Pichia anomala* (21%), *C. famata* (17%), *N. glabratus* (5%), *C. rugosa* (6%), *C. orthopsilosis* (4%), *C. kefyr* (2%), *C. lusitaniae* (2%), and *C. stellatoides* (1%). Among patients with potentially malignant lesions, the isolated species included: *P. anomala* (formerly *C. pelliculosa*) (33%), *P. kudriavzevii* (27%), *C. tropicalis* (10%), *C. famata* (9%), *C. rugosa (7%), C. guilliermondii (5%)*, C. parapsilosis (3%*), C. orthopsilosis* (3%), *C. glabrata* (1%), *C. stellatoides* (1%), and *C. intermedia* (1%). [63].

In healthy controls, the non-albicans species detected were *P. anomala* (40%), *C. tropicalis* (24%), *P. kudriavzevii* (17%), *C. guilliermondii* (4%), *C. parapsilosis* (4%), *C. orthopsilosis* (4%), *C. dubliniensis* (4%), and *C. nivariensis* (4%). A notably high prevalence of *P. anomala* was observed among healthy individuals (43.5%), followed by patients with potentially malignant lesions (33%) and those with oral squamous cell carcinoma (21%) [63].

The high frequency of oral candidiasis in patients with oral squamous cell carcinoma and potentially malignant lesions suggests a possible association between fungal infection and these clinical conditions. These findings emphasize the importance of *Candida* suppression to prevent

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opportunistic infections and potentially reduce the risk of malignant transformation of potentially malignant lesions into oral squamous cell carcinoma [61–64].

Although the presence of *Candida* is frequently observed in potentially malignant oral lesions and in established tumors, it is unclear whether this microorganism plays an active role in carcinogenesis or merely colonizes previously altered tissues. To address this question, Wang et al. [66] investigated the role of *C. albicans* in the progression of oral squamous cell carcinoma, focusing on the immunological mechanisms involved in the interaction between the fungus and the tumor microenvironment. Using in vivo experimental models, the authors demonstrated that colonization by *C. albicans* significantly enhanced tumor growth. The identified mechanism involved activation of the interleukin-17A (IL-17A) pathway and its receptor, IL-17RA. Fungal infection stimulated IL-17A production, a cytokine classically associated with antifungal immune responses, which in this context contributed to the establishment of a tumor-promoting inflammatory environment [66].

Tamgadge et al. [56] found a positive correlation between the presence of *Candida* spp. and increasing degrees of epithelial dysplasia, with a higher density of hyphae observed in more severe lesions and in cases of oral squamous cell carcinoma. These findings suggest that fungal colonization intensifies as epithelial alterations progress, indicating a possible involvement of the fungus in the evolution of potentially malignant lesions [56].

This observation is consistent with the review by Yu et al. [68], which examined recent advances in understanding the interaction between *C. albicans* and various cancers. The authors highlight that *C. albicans* may contribute to carcinogenesis through multiple mechanisms, including the induction of chronic inflammation, production of carcinogenic metabolites such as acetaldehyde, activation of pro-tumor signaling pathways (such as NF-κB and STAT3), and modulation of the tumor microenvironment. Moreover, the filamentous (hyphal) form of the fungus is considered particularly significant due to its invasive capacity and heightened inflammatory potential [68].

Taken together, these findings highlight the complex and multifaceted contribution of fungal communities to oral mucosal alterations. Although *Candida* remains the most extensively studied genus, growing evidence supports a broader model in which multiple fungal taxa, together with the bacterial microbiota and host-related factors, interact to drive the initiation and progression of these alterations.

## 5. Conclusions and Future Perspectives

This study highlights the relevance of the oral mycobiome as an essential component of human health, demonstrating that fungal communities are not merely passive colonizers but may be involved in the development of several oral diseases, including candidiasis, dental caries, periodontal diseases, dysplasia, and carcinoma. Therefore, recognizing mycobiome dynamics contributes to a more integrated understanding of oral diseases, moving beyond an approach focused exclusively on the bacteriome.

Future studies should include larger sample sizes, longer follow-up periods, and the analysis of a broader range of variables. Furthermore, it is essential to invest in the development and continuous updating of fungal ribosomal databases to enable a more comprehensive characterization of the oral mycobiome. Such advances may provide new insights into the processes of oral health and disease, contributing to the identification of innovative preventive and therapeutic strategies.

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## References


1. Belibasakis GN, Seneviratne CJ, Jayasinghe RD, Vo PT, Bostanci N, Choi Y. Bacteriome and mycobiome dysbiosis in oral mucosal dysplasia and oral cancer. Periodontol 2000. 2024 Oct;96(1):95-111. doi: 10.1111/prd.12558. Epub 2024 Mar 19. PMID: 38501658; PMCID: PMC11579824.
2. Lamont RJ, Koo H, Hajishengallis G. The oral microbiota: dynamic communities and host interactions. Nat Rev Microbiol. 2018 Dec;16(12):745-759. doi: 10.1038/s41579-018-0089-x. PMID: 30301974; PMCID: PMC6278837.
3. Hou K, Wu ZX, Chen XY, Wang JQ, Zhang D, Xiao C, Zhu D, Koya JB, Wei L, Li J, Chen ZS. Microbiota in health and diseases. Signal Transduct Target Ther. 2022 Apr 23;7(1):135. doi: 10.1038/s41392-022-00974-4. PMID: 35461318; PMCID: PMC9034083.
4. Baraniya D, Chen T, Nahar A, Alakwaa F, Hill J, Tellez M, Ismail A, Puri S, Al-Hebshi NN. Supragingival mycobiome and inter-kingdom interactions in dental caries. J Oral Microbiol. 2020 Feb 19;12(1):1729305. doi: 10.1080/20002297.2020.1729305. PMID: 32158514; PMCID: PMC7048226.
5. Hillman ET, Lu H, Yao T, Nakatsu CH. Microbial Ecology along the Gastrointestinal Tract. Microbes Environ. 2017 Dec 27;32(4):300-313. doi: 10.1264/jsme2.ME17017. Epub 2017 Nov 10. PMID: 29129876; PMCID: PMC5745014.
6. Huang H, Wang Q, Yang Y, Zhong W, He F, Li J. The mycobiome as integral part of the gut microbiome: crucial role of symbiotic fungi in health and disease. Gut Microbes. 2024 Jan-Dec;16(1):2440111. doi: 10.1080/19490976.2024.2440111. Epub 2024 Dec 15. PMID: 39676474; PMCID: PMC11651280.
7. Diaz PI, Dongari-Bagtzoglou A. Critically Appraising the Significance of the Oral Mycobiome. J Dent Res. 2021 Feb;100(2):133-140. doi: 10.1177/0022034520956975. Epub 2020 Sep 13. PMID: 32924741; PMCID: PMC8173349.
8. Diaz PI, Hong BY, Dupuy AK, Strausbaugh LD. Mining the oral mycobiome: Methods, components, and meaning. Virulence. 2017 Apr 3;8(3):313-323. doi: 10.1080/21505594.2016.1252015. Epub 2016 Oct 28. PMID: 27791473; PMCID: PMC5411240.
9. Asao K, Hashida N. Overview of Microorganisms: Bacterial Microbiome, Mycobiome, Virome Identified Using Next-Generation Sequencing, and Their Application to Ophthalmic Diseases. Microorganisms. 2025 Jun 3;13(6):1300. doi: 10.3390/microorganisms13061300. PMID: 40572188; PMCID: PMC12195238.
10. Cannon RD. Oral Fungal Infections: Past, Present, and Future. Front Oral Health. 2022 Feb 3;3:838639. doi: 10.3389/froh.2022.838639. PMID: 35187534; PMCID: PMC8850356.
11. Defta CL, Albu CC, Albu ŞD, Bogdan-Andreescu CF. Oral Mycobiota: A Narrative Review. Dent J (Basel). 2024 Apr 19;12(4):115. doi: 10.3390/dj12040115. PMID: 38668027; PMCID: PMC11049401.
12. Xu H, Dongari-Bagtzoglou A. Shaping the oral mycobiota: interactions of opportunistic fungi with oral bacteria and the host. Curr Opin Microbiol. 2015 Aug;26:65-70. doi: 10.1016/j.mib.2015.06.002. Epub 2015 Jun 19. PMID: 26100661; PMCID: PMC4577367.
13. Hong BY, Hoare A, Cardenas A, Dupuy AK, Choquette L, Salner AL, Schauer PK, Hegde U, Peterson DE, Dongari-Bagtzoglou A, Strausbaugh LD, Diaz PI. The Salivary Mycobiome Contains 2 Ecologically Distinct Mycotypes. J Dent Res. 2020 Jun;99(6):730-738. doi: 10.1177/0022034520915879. Epub 2020 Apr 21. PMID: 32315566; PMCID: PMC7243416
14. Ghannoum et al. Characterization of the Oral Fungal Microbiome (Mycobiome) in Healthy Individuals. PLoS Pathogens. 2010 Jan 8;6(1):e1000713. doi:10.1371/journal.ppat.1000713.
15. Abusleme L, Diaz PI, Freeman AF, Greenwell-Wild T, Brenchley L, Desai JV, Ng WI, Holland SM, Lionakis MS, Segre JA, Kong HH, Moutsopoulos NM. Human defects in STAT3 promote oral mucosal fungal and bacterial dysbiosis. JCI Insight. 2018 Sep 6;3(17):e122061. doi: 10.1172/jci.insight.122061. PMID: 30185668; PMCID: PMC6171814.

 doi:10.20944/preprints202604.1216.v1



16. Sedghi L, DiMassa V, Harrington A, Lynch SV, Kapila YL. The oral microbiome: Role of key organisms and complex networks in oral health and disease. Periodontol 2000. 2021 Oct;87(1):107-131. doi: 10.1111/prd.12393. PMID: 34463991; PMCID: PMC8457218.
17. Kleinstein SE, Nelson KE, Freire M. Inflammatory Networks Linking Oral Microbiome with Systemic Health and Disease. J Dent Res. 2020 Sep;99(10):1131-1139. doi: 10.1177/0022034520926126. Epub 2020 May 27. PMID: 32459164; PMCID: PMC7443998.
18. Izidoro C, Botelho J, Machado V, et al. Non-surgical periodontal treatment impact on subgingival microbiome and intra-oral halitosis. Int J Mol Sci. 2023;24:2518. doi:10.3390/ijms2403251
19. Xu H, Dongari-Bagtzoglou A. Shaping the oral mycobiota: interactions of opportunistic fungi with oral bacteria and the host. Curr Opin Microbiol. 2015 Aug;26:65-70. doi: 10.1016/j.mib.2015.06.002. Epub 2015 Jun 19. PMID: 26100661; PMCID: PMC4577367.
20. Limon JJ, Skalski JH, Underhill DM. Commensal Fungi in Health and Disease. Cell Host Microbe. 2017 Aug 9;22(2):156-165. doi: 10.1016/j.chom.2017.07.002. PMID: 28799901; PMCID: PMC5573128.
21. Sajid M, Sharma P, Srivastava S, Hariprasad R, Singh H, Bharadwaj M. Smokeless tobacco consumption induces dysbiosis of oral mycobiome: a pilot study. Appl Microbiol Biotechnol. 2022 Sep;106(17):5643-5657. doi: 10.1007/s00253-022-12096-6. Epub 2022 Aug 1. PMID: 35913514.
22. Sajid M, Srivastava S, Yadav RK, Singh H, Singh S, Bharadwaj M. Composition and Ecological Functionality of Fungal Communities Associated with Smokeless Tobacco Products Mainly Consumed in India. Microbiol Spectr. 2022 Aug 31;10(4):e0227321. doi: 10.1128/spectrum.02273-21. Epub 2022 Jun 13. PMID: 35695566; PMCID: PMC9430657.
23. Bowen WH. Dental caries—not just holes in teeth! A perspective. Mol Oral Microbiol. 2016 Jun;31(3):228-33. doi: 10.1111/omi.12132. Epub 2015 Oct 12. PMID: 26343264
24. Beall CJ, Lilly EA, Granada C, Treas K, Dubois KR 3rd, Hashmi SB, Vazquez JA, Hagensee ME, Griffen AL, Leys EJ, Fidel PL Jr. Independent Effects of HIV and Antiretroviral Therapy on the Oral Microbiome Identified by Multivariate Analyses. mBio. 2023 Jun 27;14(3):e0040923. doi: 10.1128/mbio.00409-23. Epub 2023 Apr 18. PMID: 37071004; PMCID: PMC10294613
25. Sodré CS, Rodrigues PMG, Vieira MS, Marques Paes da Silva A, Gonçalves LS, Ribeiro MG, de Carvalho Ferreira D. Oral mycobiome identification in atopic dermatitis, leukemia, and HIV patients—a systematic review. J Oral Microbiol. 2020 Aug 17;12(1):1807179. doi: 10.1080/20002297.2020.1807179. PMID: 32944157; PMCID: PMC7482892.
26. Fidel PL Jr, Moyes D, Samaranayake L, Hagensee ME. Interplay between oral immunity in HIV and the microbiome. Oral Dis. 2020 Sep;26 Suppl 1(Suppl 1):59-68. doi: 10.1111/odi.13515. PMID: 32862522; PMCID: PMC7573945
27. Cui Y, Wang Y, Zhang Y, Pang L, Zhou Y, Lin H, Tao Y. Oral Mycobiome Differences in Various Spatial Niches With and Without Severe Early Childhood Caries. Front Pediatr. 2021 Nov 15;9:748656. doi: 10.3389/fped.2021.748656. PMID: 34869106; PMCID: PMC8634708.
28. Canabarro A, Valle C, Farias MR, Santos FB, Lazera M, Wanke B. Association of subgingival colonization of Candida albicans and other yeasts with severity of chronic periodontitis. J Periodontal Res. 2013 Aug;48(4):428-32. doi: 10.1111/jre.12022. Epub 2012 Nov 8. PMID: 23137301.
29. Mathur VP, Dhillon JK. Dental Caries: A Disease Which Needs Attention. Indian J Pediatr. 2018 Mar;85(3):202-206. doi: 10.1007/s12098-017-2381-6. Epub 2017 Jun 23. PMID: 28643162.
30. Fidel PL Jr, Thompson ZA, Lilly EA, Granada C, Treas K, Dubois KR 3rd, Cook L, Hashmi SB, Lisko DJ, Mukherjee C, Vazquez JA, Hagensee ME, Griffen AL, Leys EJ, Beall CJ. Effect of HIV/HAART and Other Clinical Variables on the Oral Mycobiome Using Multivariate Analyses. mBio. 2021 Mar 23;12(2):e00294-21. doi: 10.1128/mBio.00294-21. PMID: 33758093; PMCID: PMC8092233.
31. Zeng S, Rosati E, Saggau C, Messner B, Chu H, Duan Y, Hartmann P, Wang Y, Ma S, Huang WJM, Lee J, Lee SM, Carvalho-Gontijo R, Zhang V, Hoffmann JP, Kolls JK, Raz E, Brenner DA, Kisseleva T, LeibundGut-Landmann S, Bacher P, Stärkel P, Schnabl B. Candida albicans-specific Th17 cell-mediated response contributes to alcohol-associated liver disease. Cell Host Microbe. 2023 Mar 8;31(3):389-404.e7. doi: 10.1016/j.chom.2023.02.001. PMID: 36893735; PMCID: PMC10039706.

 doi:10.20944/preprints202604.1216.v1




32. Chakladar J, John D, Magesh S, Uzelac M, Li WT, Dereschuk K, Apostol L, Brumund KT, Rodriguez JW, Ongkeko WM. The Intratumor Bacterial and Fungal Microbiome Is Characterized by HPV, Smoking, and Alcohol Consumption in Head and Neck Squamous Cell Carcinoma. Int J Mol Sci. 2022 Oct 31;23(21):13250. doi: 10.3390/ijms232113250. PMID: 36362038; PMCID: PMC9655846.
33. Fechney JM, Browne GV, Prabhu N, Irinyi L, Meyer W, Hughes T, Bockmann M, Townsend G, Salehi H, Adler CJ. Preliminary study of the oral mycobiome of children with and without dental caries. J Oral Microbiol. 2018 Oct 23;11(1):1536182. doi: 10.1080/20002297.2018.1536182. PMID: 30598729; PMCID: PMC6225480.
34. O'Connell, LM; Santos, R.; Springer, G.; Burne, RA; Nascimento, MM; Richards, VP:The specific profile of the dental mycobiome reveals strong taxonomic changes during the progression of caries in early childhood. Appl. Environ. Microbiol. 2020, 86, e02825-19.
35. Urzúa B, Hermosilla G, Gamonal J, Morales-Bozo I, Canals M, Barahona S, Cóccola C, Cifuentes V. Yeast diversity in the oral microbiota of subjects with periodontitis: Candida albicans and Candida dubliniensis colonize the periodontal pockets. Med Mycol. 2008 Dec;46(8):783-93. doi: 10.1080/13693780802060899. PMID: 18608938.
36. Xiao J, Huang X, Alkhers N, Alzamil H, Alzoubi S, Wu TT, Castillo DA, Campbell F, Davis J, Herzog K, Billings R, Kopycka-Kedzierawski DT, Hajishengallis E, Koo H. Candida albicans and Early Childhood Caries: A Systematic Review and Meta-Analysis. Caries Res. 2018;52(1-2):102-112. doi: 10.1159/000481833. Epub 2017 Dec 21. PMID: 29262404; PMCID: PMC5828948.
37. Souza JGS, Bertolini M, Thompson A, Mansfield JM, Grassmann AA, Maas K, Caimano MJ, Barao VAR, Vickerman MM, Dongari-Bagtzoglou A. Role of glucosyltransferase R in biofilm interactions between Streptococcus oralis and Candida albicans. ISME J. 2020 May;14(5):1207-1222. doi: 10.1038/s41396-020-0608-4. Epub 2020 Feb 10. PMID: 32042100; PMCID: PMC7174356.
38. de Jesus VC, Shikder R, Oryniak D, Mann K, Alamri A, Mittermuller B, Duan K, Hu P, Schroth RJ, Chelikani P. 2020. Microbiota de placas diversificada baseada no sexo em crianças com cárie grave. J Dent Res. 99(6):703–712
39. Falsetta ML, Klein MI, Colonne PM, Scott-Anne K, Gregoire S, Pai CH, Gonzalez-Begne M, Watson G, Krysan DJ, Bowen WH, Koo H. Symbiotic relationship between Streptococcus mutans and Candida albicans synergizes virulence of plaque biofilms in vivo. Infect Immun. 2014 May;82(5):1968-81. doi: 10.1128/IAI.00087-14. Epub 2014 Feb 24. PMID: 24566629; PMCID: PMC3993459.
40. Dige I, Nyvad B. Candida species in intact in vivo biofilm from carious lesions. Arch Oral Biol. 2019 May;101:142-146. doi: 10.1016/j.archoralbio.2019.03.017. Epub 2019 Mar 25. PMID: 30933902.
41. Kim D, Koo H. Spatial Design of Polymicrobial Oral Biofilm in Its Native Disease State. J Dent Res. 2020 Jun;99(6):597-603. doi: 10.1177/0022034520909313. Epub 2020 Mar 6. PMID: 32142402; PMCID: PMC7243423.
42. Thomas A, Mhambrey S, Chokshi K, Chokshi A, Jana S, Thakur S, Jose D, Bajpai G. Association of Oral Candida albicans with Severe Early Childhood Caries—A Pilot Study. J Clin Diagn Res. 2016 Aug;10(8):ZC109-12. doi: 10.7860/JCDR/2016/19387.8357. Epub 2016 Aug 1. PMID: 27656551; PMCID: PMC5028463.
43. Diaz PI, Dongari-Bagtzoglou A. Critically Appraising the Significance of the Oral Mycobiome. J Dent Res. 2021 Feb;100(2):133-140. doi: 10.1177/0022034520956975. Epub 2020 Sep 13. PMID: 32924741; PMCID: PMC8173349.
44. Du Q, Ren B, He J, Peng X, Guo Q, Zheng L, Li J, Dai H, Chen V, Zhang L, Zhou X, Xu X. Candida albicans promotes tooth decay by inducing oral microbial dysbiosis. ISME J. 2021 Mar;15(3):894-908. doi: 10.1038/s41396-020-00823-8. Epub 2020 Nov 4. PMID: 33149208; PMCID: PMC8026629.
45. Eidt G, Waltermann EDM, Hilgert JB, Arthur RA. Candida and dental caries in children, adolescents and adults: A systematic review and meta-analysis. Arch Oral Biol. 2020 Nov;119:104876. doi: 10.1016/j.archoralbio.2020.104876. Epub 2020 Aug 17. PMID: 32905885.
46. Tu Y, Zhou Z, Shu C, Zhou Y, Zhou X. The Crosstalk Between Saliva Bacteria and Fungi in Early Childhood Caries. Front Cell Infect Microbiol. 2022 Feb 14;12:845738. doi: 10.3389/fcimb.2022.845738. PMID: 35237536; PMCID: PMC8884336.

 doi:10.20944/preprints202604.1216.v1




47. Peters BA, Wu J, Hayes RB, Ahn J. The oral fungal mycobiome: characteristics and relation to periodontitis in a pilot study. BMC Microbiol. 2017 Jul 12;17(1):157. doi: 10.1186/s12866-017-1064-9. PMID: 28701186; PMCID: PMC5508751.
48. Acosta-Pagán K, Bolaños-Rosero B, Pérez C, Ortíz AP, Godoy-Vitorino F. Ecological competition in the oral mycobiome of Hispanic adults living in Puerto Rico associates with periodontitis. J Oral Microbiol. 2024 Feb 21;16(1):2316485. doi: 10.1080/20002297.2024.2316485. PMID: 38390467; PMCID: PMC10883086.
49. Sztukowska MN, Dutton LC, Delaney C, Ramsdale M, Ramage G, Jenkinson HF, Nobbs AH, Lamont RJ. Community Development between Porphyromonas gingivalis and Candida albicans Mediated by InlJ and Als3. mBio. 2018 Apr 24;9(2):e00202-18. doi: 10.1128/mBio.00202-18. PMID: 29691333; PMCID: PMC5915736.
50. Zoheir N, Kurushima Y, Lin GH, Nibali L. Periodontal infectogenomics: a systematic review update of associations between host genetic variants and subgingival microbial detection. Clin Oral Investig. 2022 Mar;26(3):2209-2221. doi: 10.1007/s00784-021-04233-8. Epub 2022 Feb 5. PMID: 35122548; PMCID: PMC8898234.
51. Könönen E, Gursoy M, Gursoy UK. Periodontitis: A Multifaceted Disease of Tooth-Supporting Tissues. J Clin Med. 2019 Jul 31;8(8):1135. doi: 10.3390/jcm8081135. PMID: 31370168; PMCID: PMC6723779.
52. Li Y, Wang K, Zhang B, Tu Q, Yao Y, Cui B, Ren B, He J, Shen X, Van Nostrand JD, Zhou J, Shi W, Xiao L, Lu C, Zhou X. Salivary mycobiome dysbiosis and its potential impact on bacteriome shifts and host immunity in oral lichen planus. Int J Oral Sci. 2019 Jul 2;11(2):13. doi: 10.1038/s41368-019-0045-2. PMID: 31263096; PMCID: PMC6802619.
53. Hu Y, Ren B, Cheng L, Deng S, Chen Q. Candida species in periodontitis: A new villain or a new target? J Dent. 2024 Sep;148:105138. doi: 10.1016/j.jdent.2024.105138. Epub 2024 Jun 19. PMID: 38906455.
54. Perera M, Al-Hebshi NN, Perera I, Ipe D, Ulett GC, Speicher DJ, Chen T, Johnson NW. A dysbiotic mycobiome dominated by Candida albicans is identified within oral squamous-cell carcinomas. J Oral Microbiol. 2017 Oct 27;9(1):1385369. doi: 10.1080/20002297.2017.1385369. PMID: 29152157; PMCID: PMC5678454.
55. Wicaksono S, Ngokwe ZB, McCullough M, Yap T. The Role of Oral Yeasts in the Development and Progression of Oral Squamous Cell Carcinoma: A Scoping Review. J Fungi (Basel). 2025 Mar 27;11(4):260. doi: 10.3390/jof11040260. PMID: 40278081; PMCID: PMC12028735.
56. Tamgadge, S.; Tamgadge, A.; Pillai, A.; Chande, M.; Acharya, S.; Kamat, N. Association of Candida Sp. com the Degrees of Dysplasia and Oral Cancer: A Study with Calcofluor White Under Fluorescent Microscopy. Irã. J. Pathol. 2017 , 12 , 348–355
57. Hebbar, P.; Pai, A.; Sujatha, D. Mycological and histological associations of Candida in oral mucosal lesions. J. Oral Sci. 2013 , 55 , 157–160.
58. Heitz-Mayfield LJA. Conventional diagnostic criteria for periodontal diseases (plaque-induced gingivitis and periodontitis). Periodontol 2000. 2024 Jun;95(1):10-19. doi: 10.1111/prd.12579. Epub 2024 Jun 3. PMID: 38831568.
59. Weerasekera, M.-M.; Wijesinghe, G.-K.; Sampath, A.; Dilhari, A.; Madhumal, T.; Dilrukshi, R.; Willaddara, R.; Karunathilaka, S.; Gunasekara, C.; Fernanda, N.; and others. The genotypes and virulence attributes of C. albicans isolates of oral leukoplakia. Med. Patol Oral. Cirugia Bucal Oral 2021 , 26 , e786–e794.
60. Belibasakis GN, Seneviratne CJ, Jayasinghe RD, Vo PT, Bostanci N, Choi Y. Bacteriome and mycobiome dysbiosis in oral mucosal dysplasia and oral cancer. Periodontol 2000. 2024 Oct;96(1):95-111. doi: 10.1111/prd.12558. Epub 2024 Mar 19. PMID: 38501658; PMCID: PMC11579824.
61. Theofilou VI, Alfaifi A, Montelongo-Jauregui D, Pettas E, Georgaki M, Nikitakis NG, Jabra-Rizk MA, Sultan AS. The oral mycobiome: Oral epithelial dysplasia and oral squamous cell carcinoma. J Oral Pathol Med. 2022 May;51(5):413-420. doi: 10.1111/jop.13295. Epub 2022 Apr 11. PMID: 35347760.
62. İlhan B, Vural C, Gürhan C, Vural C, Veral A, Wilder-Smith P, Özdemir G, Güneri P. Real-Time PCR Detection of Candida Species in Biopsy Samples from Non-Smokers with Oral Dysplasia and Oral Squamous Cell Cancer: A Retrospective Archive Study. Cancers (Basel). 2023 Nov 1;15(21):5251. doi: 10.3390/cancers15215251. PMID: 37958424; PMCID: PMC10649242.

 doi:10.20944/preprints202604.1216.v1




63. Sankari SL, Mahalakshmi K, Kumar VN. A comparative study of Candida species diversity among patients with oral squamous cell carcinoma and oral potentially malignant disorders. BMC Res Notes. 2020 Oct 20;13(1):488. doi: 10.1186/s13104-020-05336-3. PMID: 33081839; PMCID: PMC7576765.
64. Sankari, Sankar Leena; Mahalakshmi, Krishnan 1 ,.Oral Candida loading among patients with oral squamous cell carcinoma: A case-control study. Journal of Orofacial Sciences 11(1):p 55-58, jan-jun 2019. | DOI: 10.4103/jofs.jofs_69_19
65. McCullough M, Jaber M, Barrett AW, Bain L, Speight PM, Porter SR. Oral yeast carriage correlates with presence of oral epithelial dysplasia. Oral Oncol. 2002 Jun;38(4):391-3. doi: 10.1016/s1368-8375(01)00079-3. PMID: 12076705.
66. Wang X, Wu S, Wu W, Zhang W, Li L, Liu Q, Yan Z. Candida albicans Promotes Oral Cancer via IL-17A/IL-17RA-Macrophage Axis. mBio. 2023 Jun 27;14(3):e0044723. doi: 10.1128/mbio.00447-23. Epub 2023 Apr 17. PMID: 37067414; PMCID: PMC10294694.7
67. Lopes JP, Lionakis MS. Pathogenesis and virulence of Candida albicans. Virulence. 2022 Dec;13(1):89-121. doi: 10.1080/21505594.2021.2019950. PMID: 34964702; PMCID: PMC9728475.
68. Yu D, Liu Z. The research progress in the interaction between Candida albicans and cancers. Front Microbiol. 2022 Sep 28;13:988734. doi: 10.3389/fmicb.2022.988734. PMID: 36246294; PMCID: PMC9554461.
69. Singh SK, Gupta A, Rajan SY, Padmavathi BN, Mamatha GP, Mathur H, Bhuvaneshwari S, Soundarya S. Correlation of presence of Candida and epithelial dysplasia in oral mucosal lesions. J Clin Diagn Res. 2014 Oct;8(10):ZC31-5. doi: 10.7860/JCDR/2014/9872.4956. Epub 2014 Oct 20. PMID: 25478443; PMCID: PMC4253261.
70. Talapko J, Meštrović T, Dmitrović B, Juzbašić M, Matijević T, Bekić S, Erić S, Flam J, Belić D, Petek Erić A, Milostić Srb A, Škrlec I. A Putative Role of Candida albicans in Promoting Cancer Development: A Current State of Evidence and Proposed Mechanisms. Microorganisms. 2023 Jun 1;11(6):1476. doi: 10.3390/microorganisms11061476. PMID: 37374978; PMCID: PMC10305569.
71. Tasso CO, Ferrisse TM, de Oliveira AB, Ribas BR, Jorge JH. Candida species as potential risk factors for oral squamous cell carcinoma: Systematic review and meta-analysis. Cancer Epidemiol. 2023 Oct;86:102451. doi: 10.1016/j.canep.2023.102451. Epub 2023 Sep 14. PMID: 37716154.
72. Aslani N, Janbabaei G, Abastabar M, Meis JF, Babaeian M, Khodavaisy S, Boekhout T, Badali H. Identification of uncommon oral yeasts from cancer patients by MALDI-TOF mass spectrometry. BMC Infect Dis. 2018 Jan 8;18(1):24. doi: 10.1186/s12879-017-2916-5. PMID: 29310582; PMCID: PMC5759378.
73. Imabayashi Y, Moriyama M, Takeshita T, Ieda S, Hayashida JN, Tanaka A, Maehara T, Furukawa S, Ohta M, Kubota K, Yamauchi M, Ishiguro N, Yamashita Y, Nakamura S. Molecular analysis of fungal populations in patients with oral candidiasis using next-generation sequencing. Sci Rep. 2016 Jun 16;6:28110. doi: 10.1038/srep28110. PMID: 27305838; PMCID: PMC4910111.
74. Lu SY. Oral Candidosis: Pathophysiology and Best Practice for Diagnosis, Classification, and Successful Management. J Fungi (Basel). 2021 Jul 13;7(7):555. doi: 10.3390/jof7070555. PMID: 34356934; PMCID: PMC8306613.
75. Ieda S, Moriyama M, Takeshita T, Maehara T, Imabayashi Y, Shinozaki S, Tanaka A, Hayashida JN, Furukawa S, Ohta M, Yamashita Y, Nakamura S. Molecular analysis of fungal populations in patients with oral candidiasis using internal transcribed spacer region. PLoS One. 2014 Jun 30;9(6):e101156. doi: 10.1371/journal.pone.0101156. Erratum in: PLoS One. 2014;9(10):e110450. Takashita, Toru [corrected to Takeshita, Toru]. PMID: 24979710; PMCID: PMC4076276.
76. Diaconu D, Savu M, Ciobanu C, Mangalagiu V, Mangalagiu II. Current strategies in design and synthesis of antifungals hybrid and chimeric diazine derivatives. Bioorg Med Chem. 2025 Mar 1;119:118069. doi: 10.1016/j.bmc.2025.118069. Epub 2025 Jan 12. PMID: 39818112
77. Lin L, Duan W, Yu Y, Wang Y, Cao J, Li Y, Sun X, Wen S, Wang X, Guo Y, Jiang Q. Salivary mycobiome diversity at different stages of human immunodeficiency virus infection. BMC Microbiol. 2025;25:593. doi:10.1186/s12866-025-04285-w.

 doi:10.20944/preprints202604.1216.v1



78. Ieda S, Moriyama M, Takeshita T, Maehara T, Imabayashi Y, Shinozaki S, Tanaka A, Hayashida JN, Furukawa S, Ohta M, Yamashita Y, Nakamura S. Molecular analysis of fungal populations in patients with oral candidiasis using internal transcribed spacer region. PLoS One. 2014 Jun 30;9(6):e101156. doi: 10.1371/journal.pone.0101156. Erratum in: PLoS One. 2014;9(10):e110450. Takashita, Toru [corrected to Takeshita, Toru]. PMID: 24979710; PMCID: PMC4076276.
79. Mohammadi R, Morovati H, Safari F. The human mycobiome: a critical yet understudied component of health and disease. Microbiology. 2025 Dec;171(12):001631. doi: 10.1099/mic.0.001631. PMID: 41369685; PMCID: PMC12694932.