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Review

Fungi associated oral cavity hygiene and denture stomatitis: A review on diagnostic and treatment

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Abstract

Oral mucosal diseases, communications of opportunistic fungi with oral bacteria, host defense, and predisposing factors can affect oral hygiene. Denture stomatitis is a common inflammatory reaction with multifactorial etiology that is affected by oral hygiene. One of the most important factors that affect this condition is fungi, particularly *Candida albicans*. Accurate identification of etiologic agents of stomatitis at the species level is essential for selecting an effective drug and definitive treatment. The purpose of this article is to investigate the factors that are affected by oral hygiene with priority on the effect of *Candida* spp. on denture wearers.

Keywords: *Candida albicans*, Denture stomatitis, Oral hygiene

1. Introduction

A complex public of bacteria, viruses, fungi, and archaea, which live human bodies are very important to humans life [1]. The human microbes at various body sites are affected by nutrients, environmental exposure, and the immunological system [2]. Differences in properties of microbial related to the use of different dietary regimens, and medicine exposures, such as antibiotics and corticosteroids use [3, 4]. In addition, fungi like bacteria have played major roles in human health and disease [5, 6]. Culture of the fungi populating, presentation that fungi belonging to four main mycological phyla, *Ascomycota, Basidiomycota, Chytridiomycota, and Zygomycota*, (about 2–3%). Many culture-dependent examinations on human niches, from the mouth, nails, and rectum of healthy humans have isolated yeasts, such as *Candida* spp. [7]. Most studies on oral fungi have focused on *Candida* and The *Candida albicans* are the most common yeasts that causing oral disease. Oral *Candida* infection usually occurs by predisposing factors (local or systemic host factors). Decreased salivation, poor oral hygiene, wearing dentures is local factors, and diabetes mellitus, nutritional deficiency, HIV/AIDS are systemic factors. If do not pay attention to oral hygiene, wearing dentures increases the incidence of *Candida* to 60-100%. Denture stomatitis is a pathological symptom as inflammation and erythema of the oral mucosal zones exposed by the denture, which is typically linked with *Candida* species, predominantly *Candida albicans*, by reason of production biofilms on oral hole soft tissue and denture shells [8]. Diagnosis of genus and species of oral pathogenic fungi is useful for definitive therapy because fungal has a wide variety of treatments. For example, nystatin and amphotericin B, fluconazole oral suspension are used for oral candidiasis and itraconazole or ketoconazole are used for *Candida* strains resist to fluconazole. Many antifungal drugs have side effects and we need new drugs and new

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therapeutic strategies [9].

2. Factors affecting oral cavity hygiene

2.1 Interactions of fungi with oral illnesses

Some of the oral mucosal diseases present with symptoms that are pathognomonic for the condition, whereas others Oral mucosal diseases present with similar features can make identification difficult to do based on clinical examination only. These disorders are categorized based on different clinical structures, such as acute or chronic conditions, single or multiple lesions, primary or recurrent flora, and local or general disease [10, 11] (Figure 1).

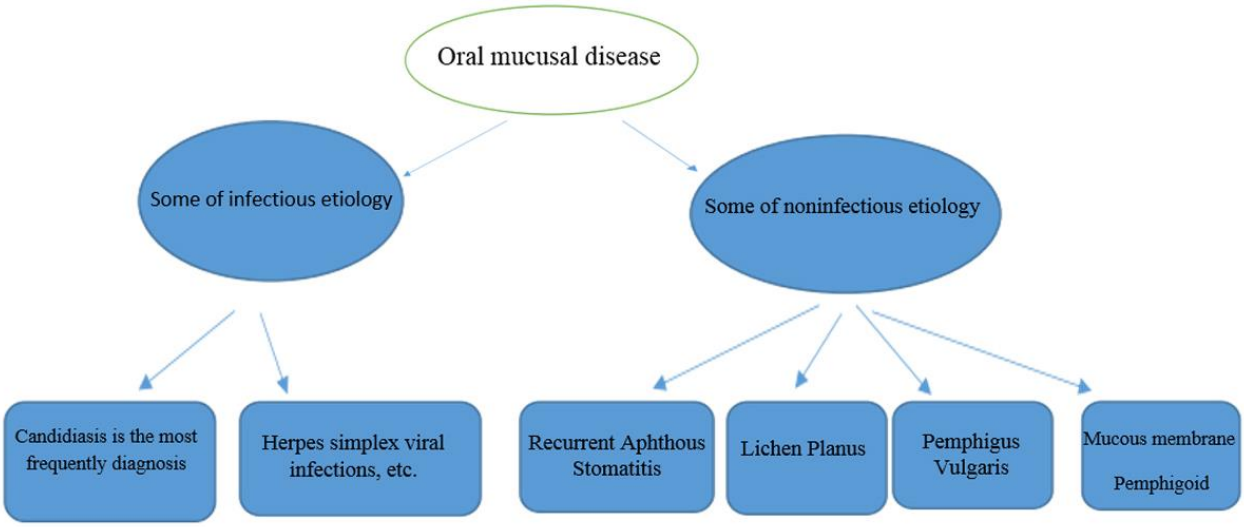

Figure 1. Infectious and noninfectious factors affecting oral cavity hygiene

Oral mucosal diseases etiology causes as result infectious and non-infectious. Oral mucosal infection diseases are less diagnosed and microbiological examinations must be done frequently. One of the most common microbiotas that reasons contamination in the oral mucosal is *Candida* spp. Although noncandidal fungal infections like aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, paracoccidioidomycosis, zygomycosis (mucormycosis), oral geotrichosis, *Rhodotorula* infection, and fusariosis are considerably less common than oral candidiasis, they can cause oral infections. More than 60% of *Candida* spp. may habitat in the human's oropharynx. *Candida* can exist in dimorphism and producing toxins for invading tissue. Several factors such as variations to saliva, dentures, drug, nutritional deficiencies, and immunosuppressive diseases, make an individual *Candida* infection. The most common kinds of clinical conditions in the human oropharynx are pseudomembranous candidiasis (Angular cheilitis), epithelial cell desquamation, and necrotic tissue. Erythematous (atrophic) candidiasis, which is frequently related with the use of corticosteroids, broad-spectrum antibiotics, and chronic hyperplastic candidiasis are other kinds of clinical conditions [11].

2.2 Interactions of opportunistic fungi with oral bacteria

A healthy oral cavity has dissimilar bacterial, viral, and fungal species. Maximum are also commensal species, but they can become pathogenic in response to variations in the environment and personal hygiene. Bacteria have synergistic communications on biofilms production through their secretory molecules. These secretory molecules are Acyl-homoserine lactones, peptide autoinducers, autoinducers-2 (AI-2), which have been identified in bacteria and fungi [12]. The peptide autoinducers are the most predominant in the oral cavity. Human oral microbiome genetics are an influence on oral viruses, bacteria, and fungi. Metagenomics technologies can help to identify strains causing biofilm in the oral cavity [13]. The fungi's role in the oral cavity is mainly indefinite and interactions with bacteria can affect oral health. About 600 bacterial species and many of fungal species live the oral cavity of humans. Most

study on oral molds has focused on *Candida* species. Study on the oral mycobiome by molecular characterizations showing the great variety of fungi inhabit in the oral cavity sequencing of 16S rRNA and internal transcribed spacer 1 (ITS1)-based amplicon library can let rapid identification of bacteria and fungi species in oral samples [14]. Oral fungus is an significant part of the oral microbiota that has received increased consideration. The variety of the fungal community in the oral cavity is significantly higher than any other body site. Any difference of local mold groups in immunosuppressed people could be produced oropharyngeal fungal infections. Variations in the human location are essential in developing fungal diseases and communication between fungi, bacteria and host can affect the formation of oral cavity infection [15-17]. Entering ecological fungi via food intake and mouth breathing can increase the diversity of fungal in the oral cavity. Among fungi, *Candida* species, and among bacteria, the *Streptococcus* assortment (including *Streptococcus gordonii, Streptococcus oralis, and Streptococcus sanguinis*) have identified more than another microbiota [18]. Signaling, metabiotic and physical adhesion molecules between those can influence fungal growth, gene expression, and pathogenicity. Fungal O-Mannosyl and bacterial and fungal soluble α- and β-glucans cause co-aggregation interactions [19, 20]. This interaction also augmented the harshness and incidence of oral candidiasis lesions and mucosal inflammatory responses, resulting in amplification of Toll-like receptor 2 (TLR2) and neutrophilic response [21].

2.3 The commonest fungi in oral infections

Among the mycobiota in the healthy human oral cavity, 74 cultivable and 11 no cultivable fungal genera are identification, which comprises *Candida* species (*C. Albicans, C. parapsilosis, C. tropicalis, C. khmerensis, and C. metapsilosis*), *Cladosporium*, *Aureobasidium*, *Saccharomycetales*, *Aspergillus*, *Fusarium* and *Cryptococcus* [22]. *Aspergillus, Fusarium, Cryptococcus, and Cladosporium*, are human pathogens. The 60 nonpathogenic molds noticed in the oral rinse samples in the form of spores from the air or food. Recently, *Malassezia* spp. in the saliva of healthy detected with sequencing analysis of ITS1 amplicons [23]. Conventional and molecular methods identified 144 isolates of *Candida* species. Among the *C. Albicans* complex, neither *C. stellatoidea* nor *C. Africana* was identified by HWP1 gene amplification. Subsequently, other isolates were identified and confirmed with MALDI-TOF at the species level [24]. *Geotrichum* spp. is a commensal fungus in humans and no studies have reported that this fungus is the normal oral. This fungus has affected the respiratory tract (bronchi, lungs), superficial skin infections, invasive infection in immunosuppressed patients, and cause oral geotrichosis associated with diabetes mellitus [25]. Mucormycosis is an invasive fungal infection that can develop in immunocompromised patients. It is caused by periorbital infection and meningoencephalitis in patients with uncontrolled diabetes [26]. Paracoccidioidomycosis (PCM) is one of the most frequent systemic fungal infections that cause oral lesions and may affect the gingiva, buccal mucosa, hard palate, lips, and tongue [27].

2.4 Host defense against oral fungal infection

The antifungal intrinsic immune cells are mainly phagocytes, including neutrophils and macrophages, and epithelial and endothelial cells, which eliminate mycobiota through phagocytosis and direct pathogen killing [28, 29]. Neutrophils, migrating from the blood vessels to the affected tissue, are the first cells that killing mycobiota by the oxidative burst and proteases [27]. Therefore, the oral epithelium is able to secrete a variation of protection effector molecules. In early and later life, mucosal and cutaneous fungal infections are increasing worldwide, especially with oral candidiasis. TLRs are receptors that recognize conserved pathogen-associated molecular patterns (PAMPs), like bacterial, viral, or fungal antigens. C-type lectins are other receptors (CLRs) that recognize carbohydrates found in the fungal cell wall, including mannose (the mannose receptor-MR), β-glucan (Dectin-1), mannans (Dectin-2, -3), and chitin (receptor unknown). Most TLRs communicated in oral epithelial cells, healthy epithelial tissue, and oral mucosa from patients with oral candidiasis [28]. Saliva in the oral cavity is immune modulators host defense against oral fungal infections. Secretory immunoglobulin A (sIgA) is an abundant antibody produced by salivary glands and secreted in saliva, and it has multiple roles in mucosal immunity. Salivary histatin 5 (Hst 5) is the main antifungal protein synthesized by human salivary glands.

Another antifungal protein in the oral cavity are LL-37. It is a gene encoding for the only member of the human cathelicidin family, created by neutrophils or mucosal tissues. Calprotectin is another antifungal protein, produced by mucosal keratinocytes that have synergistic activity in the presence of lactoferrin. Both of these proteins decrease fungal growth by withholding important metal nutrients from *C. Albicans*. Lysozyme with the potential to candidacidal activities in saliva produces by oral neutrophil leukocytes [21]. Activation of TLRs is an anti-inflammatory that helps to homeostasis. IL-6, IL-1β, TGFβ, and IL-23 cause arise in Th17 cells. These cells express IL- 17 (IL-17A) in addition IL-17F, IL-21 IL-22 and GM-CSF [30]. Dendritic cells (DCs) can uptake fungi and stimulates the diversity of innocent T cells into effector Th-cell subtypes like Th17 [7]. *C. albicans* express primes Th17 cells that produce IL-17 and IFN-γ, but not IL-10. Antimicrobial peptide (AMP) production in the oral cavity can help to fungi elimination. IL-17 is very important in reaction to *Candida* at mucosal surfaces. This mediator protective neutrophil influx and AMPs via collaboration to control overgrowth and switching of *Candida* to invasive form [30].

3. Predisposing factors for fungal oral infection

3.1 Systemic host factors

One of the main risk factors for mycotic infections that reason morbidity or mortality among hemodialysis and post-transplant patients is diabetes mellitus (Endocrine disorders). A high level of glycemic can lessen salivary flow and pH, increase salivary glucose level, and facilitate oral candidiasis like middle glossitis, atrophic glossitis, denture stomatitis, and angular cheilitis. Non *Albicans* species like *Pichia*, *Trichosporon*, *Geotrichum* can recognize in poorly controlled diabetes patients. Removable prostheses and cigarette smoking in diabetic patients can cause a higher rate of fungal infections [31].Oral candidiasis is associated with autoimmune disorders like Sjögren's syndrome (Exocrine disorders). In this syndrome, the salivary gland has dysfunction (hyposalivation based on unstimulated and stimulated flow rates) that causes oral complications [32, 33]. Autoimmune disease focused on T cells that increasing chronic fungal infection [34]. Innate and adaptive T-helper cells are essential to the protection and prevent the expansion of fungal infection in the human body. A mutation in the autoimmune regulator (AIRE) gene in the thymus, a transcriptional factor, regulates the expression of cytokines and chemokines in medullary thymic epithelial cells (mTECs), that essential for selecting proper T-cell (helper (CD4) and cytotoxic (CD8) T cells). Lack of mTECs permits the autoreactive T cells, stimulates tissue injury, and make systemic inflammation [17]. When the host immune system agonizes, like immunodeficiency, *C. albicans* can become invasive and involving the oral cavity and other locations in the body [35]. Over 60% of HIV-ill patients and more than 80% of patients detected with AIDS, infected by *Candida* spp. Among the disease in which candidiasis occurs can be mention immunodeficiency syndrome, DiGeorge syndrome, hereditary myeloperoxidase deficiency, and Chediak-Higashi [36-38]. One of the predisposing factors in elderly people that cases of oral infection is kidney's disease that occurs by treatments with antibiotics and sulphonamides. Alcoholism, high caffeine use, chronic hepatitis C virus, HIV infection, diabetes mellitus, and other metabolic illnesses can reason xerostomia that reduces the salivary flow in elderly patients. These disorders are predisposing factors to the virulence of the *Candida* species and affect oral hygiene and denture wearing [39, 40]. Cytotoxic chemotherapy and radiotherapy in solid organ or hematological malignancies are the leading cause of 30 to 94% oral candidiasis. Prophylaxis with antifungal medicines is very important to prevent oral mycosis. However, nystatin appears ineffective in these patients [41]. Iron and folate, vitamin C, B12, and A deficiencies, cause to reduced host defenses, and on the other hand, carbohydrate-rich diets are a risk factor that to increases the adherence of *Candida* species to epithelial cells [42]. Broad-spectrum antibiotics, immunomodulatory and xerogenic drugs, and drugs cause xerostomia (dry mouth) side effects, like corticosteroids, antidepressants, antipsychotics, anticholinergics, antihypertensives, and antiadrenergic can predispose to oral candidiasis [43]. Cell-mediated immunity, which is defense against *Candida* infection, declines with advancing age. Oral environmental factors and age are associated with microbes in the saliva because aging makes a proliferation in the concentration of microorganisms in saliva [44].

3.2 Local host factors

Mechanical trauma like a unwell fitting denture and saliva increases the risk of tissue diffusion and colonization by *Candida* and *Candida* infection is responsible for the pathogenesis of the denture stomatitis [45]. Saliva is very important in innate immunity because including lysozyme, hystatin, lactoferrin, calprotectin, and IgA. On the other hand, salivary protein as the mucinous and the Catherine is like adhesion receptors that detected the mannoproteins present in the *Candida* species. Saliva disorder with xerostomia induces the variation of the normal microbial and level of pH [39]. The flow of saliva eliminates the carbohydrates in the food that help the biofilm creation of *Candida* yeasts on denture acrylic materials and neutralized pH levels that are decreased by bacteria, via the saliva buffering activity thus wasted nourishing source to the *Candida* spp. Denture age is an important factor for the accumulation of colonization *Candida* in acrylic materials. Only 25% of dentures for less than a year were detected with denture stomatitis and over 84% more than five years had the disease [39, 46]. Stimulants in the denture that playing an important role in causing allergic with continuous denture wearing at night are two other predisposing factors that cause disease in the oral cavity [38].

3.3 Other factors

Several studies have been shown tobacco smoking, alone and with other systemic or local factors, can increase oral *C. albicans* and *Streptococcus mutans* adhesion that resulting biofilm in the denture. Studies have established that the H antigen in the blood group is a receptor for *Candida albicans*. Thus, people with blood group O that have more H antigen on their cell surfaces may be at higher risk of increasing oral candidiasis. Moreover, candidiasis is associated with gender and has been reported higher in women compared to men, and this connection would be increasing during pregnancy [41, 47].

4. Diagnostic of oral fungal infection

The identification of oral candidiasis is based on clinical diagnosis with a medical history. Oral fungal infection presents in one of two forms: erythematous or white. Erythematous is characterized by lesions that are red, including acute atrophic candidiasis, chronic atrophic candidiasis, median glossitis, angular cheilitis, and linear gingival erythema. White is characterized by lesions that are white, including pseudomembranous candidiasis and hyperplastic candidiasis [48]. Laboratory tests of clinical specimens include: direct microscopy test (using 10% potassium hydr oxide (KOH)), rapid staining (Giemsa or gram staining), Gomori-Grocott methenamine silver (GMS) staining (the main staining for tissue samples in mycology), culture on the selective medium (especially Sabouraud dextrose agar (SC) containing chloramphenicol or gentamycin and Sabouraud dextrose agar containing chloramphenicol and cycloheximide (SCC)), the germ tube test, the enzyme techniques (chromogenic media), the immunological diagnostic techniques and the collection of saliva and incisional biopsy [49]. The genetic methods offer high sensitivity and specificity, and allow identification of the pathogen without having to perform cultures. Additionally, samples from patients getting antifungal treatment can be used. However, these methods are more expensive and are not available in most hospital centers. Molecular methods include: polymerase chain reaction (PCR), nucleic acid sequence-based amplification (NASBA), amplified fragment length polymorphism (AFLP), randomly amplified polymorphic DNA (RAPD) analysis, and MALDI-TOF MS-based. These identifications may be useful for definitive antifungal therapy [8, 24]. According to the American Academy of Oral and Maxillofacial Pathology, any atypical tissue must be biopsy for a microscopic examination that is the gold standard for the diagnosis of most lesions. Any lesion from the oral cavity, if continuing for more than 2 weeks should be sent for the histopathological exam. Oropharyngeal candidiasis like acute pseudomembranous, acute atrophic, chronic atrophic, chronic hyperplastic, and angular cheilitis need used to swabs and oral rinse samples for smear preparation and culture for diagnosing candidiasis [50]. For chronic hyperplastic candidiasis (CHC), histopathologic examination shows parakeratosis, neutrophilic micro-abscesses, a thickened spinous layer, and chronic inflammation of the underlying connective tissue associated with long-standing *Candida* infection of the mucosa. The *Candida* hyphae are embedding in the parakeratin into the viable cell layers of the epithelium. A biopsy of abnormal tissue is generally advisable (PAS staining is

used). About 35% of CHC cases show a mainly "mucosal" reaction pattern, 25% show features of squamous epithelial dysplasia, mild or moderate grade, and in some cases, dyskeratosis affecting all the keratinocyte cell layers. Re-biopsy after antifungal therapy is suitable because this is possible that the *Candida* infection is superimposed on an innate dysplastic lesion [51].

5. Prevention and treatment

The treatment of candidiasis is difficult due to the recurrence, the limitation of antifungal drugs, and their side effects. The common antifungal mediators for the management of oral candidiasis are topical (Nystatin, amphotericins, miconazole, clotrimazole) and systemic (Ketoconazole, fluconazole, itraconazole) management [8, 52]. Posaconazole, ravuconazole, and echinocandins such as caspofungin, micafungin, and anidulafungin are newer antifungals in the prophylaxis [53]. The patient's therapeutic history, oral signs, and Laboratory testing of clinical specimens include direct microscopy tests, culture and biopsy can help to the diagnosis of oral microbiota and drug choice [41]. Identification of species is essential for rapid treatment [45]. Nystatin is the primary typical treatment for denture stomatitis [43, 54], but ineffective for candidal lesions in cancer patients [53].For the treatment of fungal angular cheilitis (with *Candida* priority) must be used to nystatin cream, or miconazole cream (2%), or clotrimazole cream (1%) [55]. If these treatments are unsuccessful, systemic antifungal agents should be used. On the other hand, the prolonged or frequent use of antifungal medicines is a major problem for the development of resistant species. Moreover, therapeutic drug levels are important, especially in patients with reduced saliva production [56]. Regardless expend the systemic antifungal medicine; the use of a contaminated denture can be recurrence oral candidiasis [8, 44, 57]. Denture base material, age of denture, age of patients, gender, and dietary factors (high carbohydrate diet, vegetarian diet consisting of vegetables, fruits, cereals, and pulses) are very important for denture hygiene. One of the important methods for denture hygiene is chemical (antimicrobial cleansing agent) and mechanical (brushing, sonic vibrators, and ultrasonic) methods. The use of toothbrushing, mouthwashes, and cleaning tablets for acrylic denture overnight storage can be alone effective in reduces denture biofilm mass and treating denture stomatitis [39, 42, 58]. Use of pre-coating biomaterials (silicone rubber or denture acrylic) with chemicals resources (silanes, chlorhexidine, histatins, metal nanoparticles (TiO2, Fe2O3, AgNPs)) is the strategy to decrease the adhesion and constrain the growth of *Candida* [58, 59]. Alkaline peroxides, alkaline hypochlorite acids, and Chlorhexidine gluconate are disinfectant agents, that have inhabited bacteria, viruses, and fungi infection and denture biofilm formation [52], but used the combination with nystatin, reduced efficacy of nystatin [39, 58]. Sodium hypochlorite (NaOCl) is a gold standard solution but not be used always. Citric acid, immediately after treatments, can be active in decreasing *C. albicans* cell viability in a biofilm [60, 61]. However, these disinfectant agents do not completely take out the biofilm and do not prevent its formation after 48h [62]. Another technique that can be used not only to sterilize but also for the cure of denture stomatitis is Microwave irradiation that demonstrated to be safe, simple, easy to use, effective, and low-cost [46]. This method does not induce resistance for fungi and it seems not to alter the color or smell of the dentures [63] and prevents the unwanted effects due to antifungal drugs, such as nausea, vomiting, and hepatotoxic and nephrotoxic effects [46]. This method is effective against microorganisms via 650 W of microwave irradiation for 3 minutes [42, 63]. Essential oils of plants are a new trend in treatment. Eugenol, linalool, menthol, farnesol, menthone, geraniol, terpine-4-ol, α-terpineol, and tyrosol, carvacrol have durable antifungal activity *in vitro* [55]. Moreover, garlic has biological effects with a deficiency of side effects so it could be a replacement for nystatin in oral candidiasis [8, 43]. Probiotic bacteria such as *Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* LC705, *Propionibacterium freudenreichii,* and *Shermanii* JS can reduce the growth of pathogenic microbes like *Candida* spp. in the oral cavity [53]. One of the preventive treatments for denture stomatitis is combination antifungals (nystatin, amphotericin, fluconazole, clotrimazole) with thin-film polymer materials that could be inhibiting *C. Albicans* biofilm growth in denture materials [56]. Furthermore, conjugation nanoparticles (like silver-zinc zeolite) with thin-film polymer materials exhibited that the

biofilm formation will be lesser [59].

6. Conclusions

Denture stomatitis is the inflammatory response that is generally seen in oral cavity hygiene and dental studies. Systemic and local host factors are predisposing factors for fungi infections. *C. Albicans* is the most common microbe species capable of producing infection at several anatomical locations and its diagnosis is significant to the choice of antifungal therapy. Direct microscopy tests and culture with metagenomics technologies are the best methods that can help to identify strains causing biofilm in the oral cavity. On the other, the limitation of antifungal medicines, and their side effects are the most common problems for the treatment of candidiasis. Use of essential oils and probiotic bacteria in the oral cavity, and use of combination antifungals or nanoparticles with thin-film polymer materials could be inhibited *C. albicans* biofilm growth on denture materials that recommended.

Author contributions

All authors contributed equally to this manuscript and approved the final version of the manuscript.

Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical declarations

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