

Review

# Biomaterials for the Prevention of Oral Candidiasis Development

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**Abstract:** Thousands of microorganisms coexist within the human microbiota. However, certain conditions can predispose the organism to the overgrowth of specific pathogens that further lead to opportunistic infections. One of the most common such imbalances in the normal oral flora is the excessive growth of *Candida* spp, which produces oral candidiasis. In immunocompromised individuals, this fungal infection can reach the systemic level and become life-threatening. Hence, prompt and efficient treatment must be administered. Traditional antifungal agents, such as polyenes, azoles, and echinocandins, may often result in severe adverse effects, regardless of the administration form. Therefore, novel treatments have to be developed and implemented in clinical practice. In this regard, the present paper focuses on the newest therapeutic options against oral *Candida* infections, reviewing compounds and biomaterials with inherent antifungal properties, improved materials for dental prostheses and denture adhesives, drug delivery systems, and combined approaches towards developing the optimum treatment.

**Keywords:** fungal infections; oral candidiasis; antifungal drugs; anti-*Candida* compounds; antifungal biomaterials

## 1. Introduction

The oral microbiota is a normal part of the oral cavity, including several hundred to several thousand different microorganisms. Its role is to protect against colonization of extrinsic infectious agents, which could affect the overall health [1]. However, under certain circumstances, oral infections can occur. Poor oral hygiene, malnutrition, use of antibiotics, trauma, endocrinopathies, and use of removable prosthesis are only a few of the factors that favor infections by invasive fungal pathogens [2–4].

*Candida* species represent a class of such pathogens. In healthy individuals, *Candida* is a harmless organism found in the mucous membranes such as ears, eyes, nose, mouth, gastrointestinal tract, reproductive organs, and skin. In immunocompromised patients, it becomes overgrown, causing opportunistic infections, with symptoms varying from mild localized rashes to severe disseminated infections. *Candida* infections are known as candidiasis (sometimes found in the literature as candidosis), the *Candida* infections localized in the oral cavity being generally termed oral candidiasis [4–8].

Oral candidiasis affects the intraoral, pharyngeal, and perioral regions, being a frequent source of discomfort, pain, loss of taste, and aversion to food [9,10]. Moreover, when

the immune system is weakened or a disruption in the host environment, there is a risk of tracheal or esophageal extension and even systemic dissemination, which may be life-threatening [6,11,12].

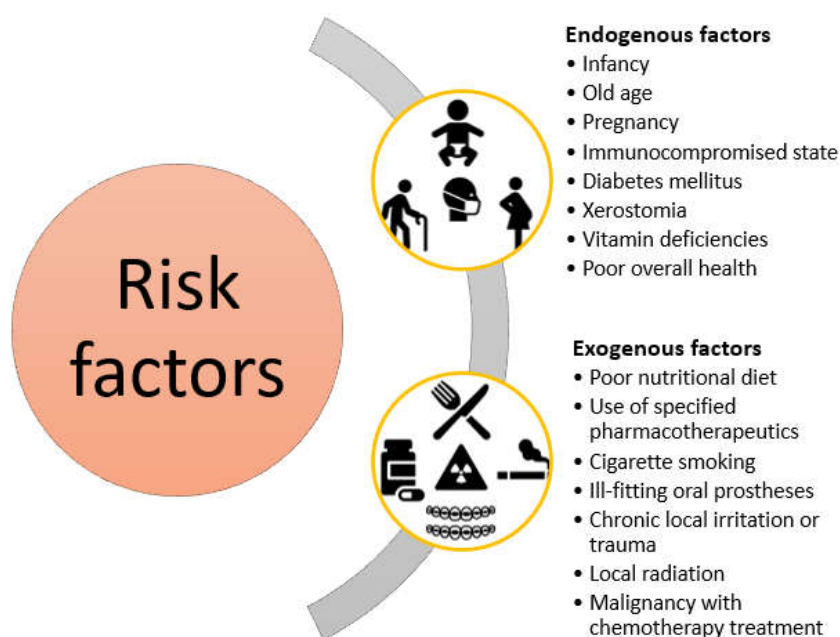
Oral candidiasis treatment consists of the administration of conventional antifungal agents. Nonetheless, the efficiency of this approach is impaired by the emergence of drug-resistant *Candida* species. Hence, new therapeutic strategies have to be developed [7].

In this respect, this paper reviews oral candidiasis from the perspectives of causative pathogens, risk factors, and classic treatment options, further focusing on novel alternatives against *Candida* infections. Specifically, there are extensively described intrinsic anti-*Candida* compounds and biomaterials, replacements for classic prostheses and adhesives materials, controlled release drug-delivery systems, and combinations of these strategies to obtain optimum treatment.

This review aims to thoroughly present the state of the art of oral candidiasis to set a clear context for future research. Explicitly, through a deep understanding of the current and developing treatment options, better solutions can be envisaged for preventing the overgrowth of drug-resistant *Candida* species.

## 2. Causative Pathogens and Risk Factors

*Candida* is a genus of yeast fungus belonging to the division Ascomycota [13] that can exist both as a commensal organism and an opportunistic pathogen in the human body [10,14–16]. *Candida* species are normal microbiota components of the mucosal oral cavity, gastrointestinal system, and genitourinary tracts [17]. When there is an imbalance in the normal oral flora, the overgrowth of *Candida* spp. may occur, thus producing oral candidiasis [5]. *Candida* spp. are present as yeasts in a healthy state, but under certain conditions, may transform into a pathogenic hyphael form [10]. The predisposing factors of oral candidiasis development include immune dysfunctions, immune suppressant drugs, prolonged antibiotic therapy, xerostomia, diabetes, human immunodeficiency virus (HIV) infection, chemotherapy, radiotherapy, alcohol and tobacco use, and dental prostheses [10,17–19] (Figure 1).

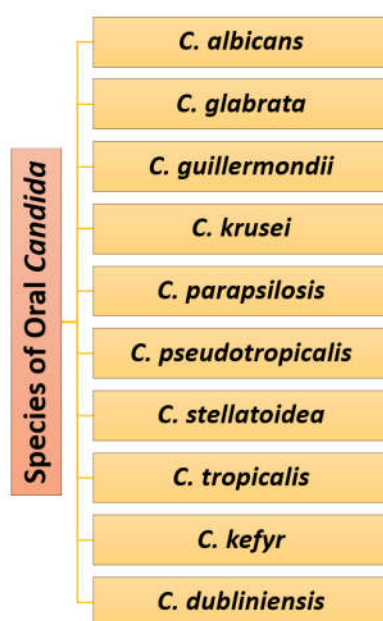


**Figure 1.** Classification of risk factors associated with oral candidiasis development. Created based on information from literature references [6,10,17–20].

*Candida* is one of the most common causes of fungal infections worldwide, being responsible for more than 400,000 infections annually [21]. The incidence of candidiasis has increased recently due to the aging population and growing numbers of immunocompromised patients [22].

Out of the *Candida* species, *Candida albicans* is considered the primary causative pathogen of oral candidiasis [14,17,23]. This is due to its high capability of adherence to oral tissues and denture surfaces, resulting in biofilm formation [14,24]. *C. albicans* is also the most virulent pathogenic *Candida* species, accounting for 70–80% of isolates from oral mucosal lesions [25].

Oral candidiasis can be also caused by non-*albicans Candida* species. Microorganisms like *C. glabrata*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, *C. pseudotropicalis*, *C. stellatoidea*, *C. tropicalis*, *C. kefyr*, and *C. dubliniensis* are also responsible for oral infections, becoming more prevalent and important opportunistic pathogens in immunocompromised patients [5,14,22,26–29] (Figure 2). Moreover, some of these species have intrinsic resistance to antifungals (e.g., *C. glabrata* and *C. krusei*) and/or rapidly develop such resistance (e.g., *C. parapsilosis* and *C. tropicalis*) [12,30].



**Figure 2.** *Candida* spp. causing oral candidiasis. Created based on information from literature references [5,10,14,17,22,26–28].

Identifying the responsible pathogen for the infection is essential for choosing the best-suited antifungal agent, as susceptibility to different drugs varies between *Candida* species (Table 1).

**Table 1.** Comparison of in vitro susceptibilities of different *Candida* species to conventional antifungal agents. Adapted from [29], BMC Infectious Diseases, 2018

| <div>Antifungal Agent</div> <div>Candida Species</div> | Amphotericin |                   |                   | Fluconazole |                   |                   | Anidulafungin |                   |                   | Caspofungin |                   |                   |
|--|--------------|-------------------|-------------------|-------------|-------------------|-------------------|---------------|-------------------|-------------------|-------------|-------------------|-------------------|
|  | MIC Range    | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC Range   | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC Range     | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC Range   | MIC <sub>50</sub> | MIC <sub>90</sub> |
| <i>C. albicans</i>                                     | 0.016–16     | 1                 | 4                 | 0.063–64    | 0.5               | 8                 | 0.008–0.25    | 0.031             | 0.125             | 0.008–8     | 0.25              | 1                 |
| <i>C. dubliniensis</i>                                 | 0.063–0.125  | 0.031             | 2                 | 0.063–0.125 | 0.125             | 0.125             | 0.008–0.125   | 0.125             | 0.25              | 0.25–2      | 0.5               | 2                 |
| <i>C. glabrata</i>                                     | 0.016–4      | 1                 | 2                 | 0.25–64     | 8                 | 64                | 0.016–1       | 0.063             | 1                 | 0.008–2     | 0.5               | 2                 |
| <i>C. krusei</i>                                       | 0.063–2      | 0.5               | 1                 | 0.25–64     | 8                 | 64                | 0.016–0.25    | 0.125             | 0.25              | 0.063–4     | 2                 | 4                 |
| <i>C. tropicalis</i>                                   | 0.031–2      | 1                 | 2                 | 0.063–8     | 4                 | 8                 | 0.008–0.063   | 0.063             | 0.063             | 0.031–8     | 0.5               | 8                 |
| <i>C. keyfr</i>  | 0.016–1      | 0.5               | 1                 | 0.25–32     | 4                 | 32                | 0.031–0.063   | 0.063             | 0.5               | 0.125–0.05  | 0.25              | 0.5               |

MIC—minimum inhibitory concentration (µg/mL).

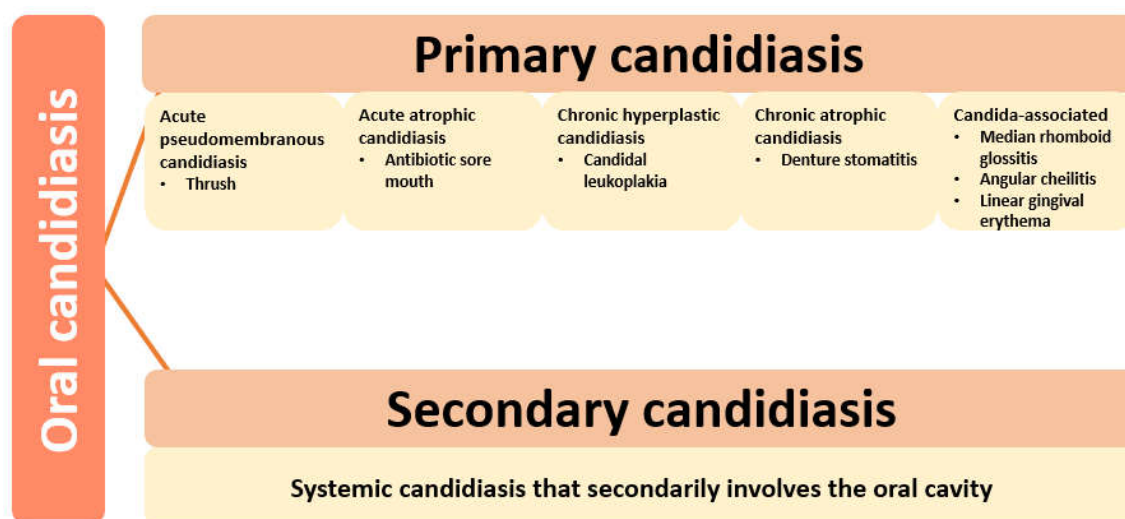
Besides, *Candida* spp. may further interact with various microorganisms within the mouth, leading to a complex and mixed biofilm with an organized structure that is difficult to remove [24]. Pathogens accumulation on the host's mucous membranes, acrylic surfaces of removable orthodontic devices, and denture prostheses results in the production of proteolysis enzymes that damage mucosal cells [18]. Hence, there is created a dangerous focus of inflammation that increases the risk of cerebral strokes, decompensated glycemia, and focal and autoimmune diseases [17]. Coupled with their drug resistance, biofilms lead to challenges in developing therapeutic approaches to prevent and cure oral infections [13].

Severe fungal infections have been especially reported in HIV infected individuals, patients undergoing hematopoietic stem cell transplantation, and those receiving intensive chemotherapy and radiotherapy. In particular, the latter factors facilitate fungal overgrowth as they modify the physiology and microbial ecology of the oral environment to prolonged xerostomia and hyposalivation. Moreover, due to the compromised immune defense mechanisms, systemic infections may occur, thus resulting in significant patient morbidity [29]. To avoid infection generalization, prophylaxis treatment against *Candida* can be provided to predisposed patients. However, it must be proceeded with care as, in hematological malignancies and stem cell transplant recipients, a microbiota imbalance may occur, and *Aspergillus* and other molds may overgrow to produce dangerous fungal infections instead [31].

### 3. Classic Treatment Options

In denture wearers, oral candidiasis' current management relies on good hygiene practices, close attention to proper denture fit with tissue conditioners/liners/rebases, and administration of antifungal drugs [20]. Immunocompetent patients respond well to topical or oral medications, but there is a high risk of systemic infection in the case of the elderly and medically or immunologically compromised patients [4].

Depending on the affected tissues, oral candidiasis can be classified into primary and secondary. Primary candidiasis refers to infections that only involve oral or perioral tissues, while secondary candidiasis is a systemic *Candida* infection that collaterally affects the oral cavity [6]. Based on the clinical manifestations, primary oral candidiasis can be further divided into several subclasses, as presented in Figure 3.



**Figure 3.** Types of oral candidiasis. Created based on information from literature references [6,14,32].

Depending on the type of oral candidiasis, several treatment options can be employed (Table 2). The most conventional and efficient currently available drugs for treating oral candidiasis are polyenes (e.g., amphotericin B and nystatin), azoles (e.g., miconazole, clotrimazole, fluconazole, itraconazole, voriconazole, posaconazole, and ketoconazole), and echinocandins (e.g., anidulafungin, caspofungin, and micafungin). These antifungal agents can be administered either locally or systemically, in various forms ranging from oral suspensions, ointments, creams, gels, and troches, to tablets, pastilles, and even intravenous infusions. However, due to their toxicity, adverse side effects, and acquired resistance, these therapeutics action is often hindered [7,8,15,19,22,27,33–35].

**Table 2.** Antifungal medication.

| Drug           | Form              | Dose                 | Indication   | Adverse Effects  | Refs.      |
|----------------|-------------------|----------------------|--|--|------------|
| Amphotericin B | Infusion          | 100–200 mg/6 h       | Intraoral candidiasis, chronic erythematous candidiasis  | Renal, cardiovascular, spinal and neurological effects       | [10,36,37] |
|                | Suspension        | 4–6 mL/6 h           | Intraoral candidiasis  | Well tolerated   | [10,36]    |
|                | Ointment          | 2–4 applications/day | Angular cheilitis  | Well tolerated   | [10,36]    |
| Nystatin       | Tablets/Pastilles | 2 every 8 h          | Denture stomatitis   | Uncommon effects: nausea, vomiting, gastrointestinal effects | [36,38]    |
|                | Tablets           | 50–100 mg/day        | Pseudomembranous candidiasis, acute erythematous candidiasis, chronic hyperplastic candidiasis | Nausea, vomiting, diarrhea, abdominal pain                   | [36,37]    |
| Fluconazole    | Suspension        | 10 mg/mL             | Oropharyngeal candidiasis  | Nausea, vomiting, diarrhea, abdominal pain                   | [36,37,39] |
| Miconazole     | Gel/cream         | 100 mg/6 h           | Angular cheilitis, chronic erythematous candidiasis  | Uncommon effects: burning, irritation, nausea, diarrhea      | [10,36,37] |
| Ketoconazole   | Gel/cream         | 3 times/day          | Angular cheilitis  | Nausea, vomiting   | [10,36]    |
|                | Tablets           | 200 mg, 2–2/day      | Pseudomembranous candidiasis, acute  | Abdominal pain   | [36,37]    |

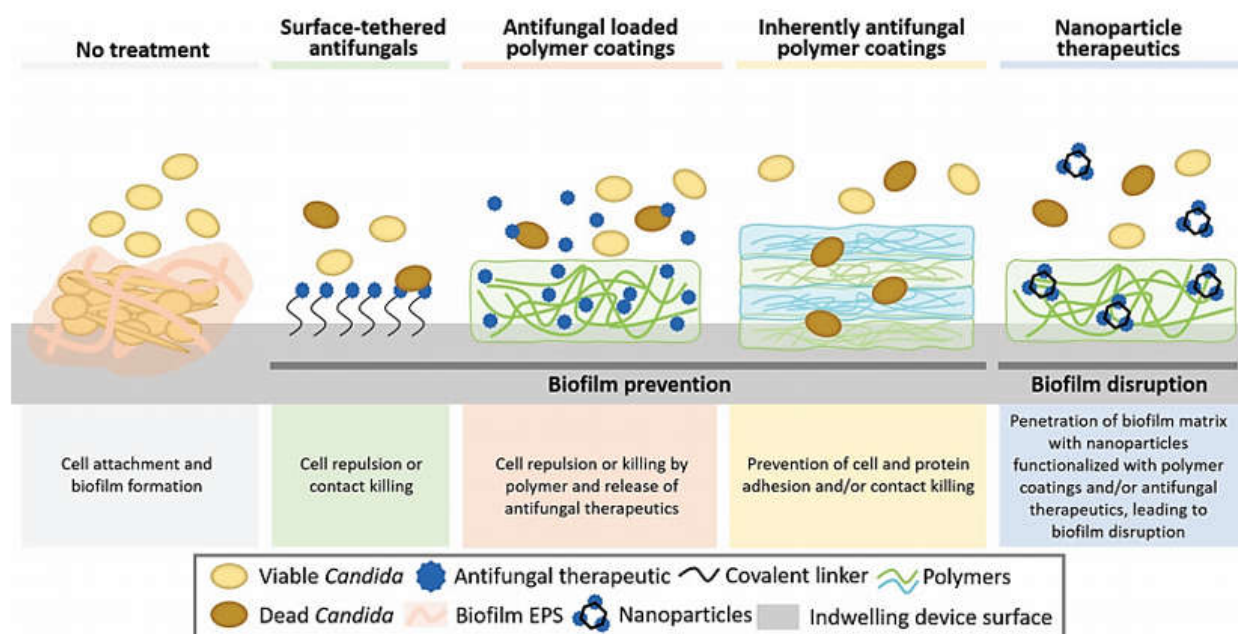
| Drug                                    | Form                    | Dose   | Indication   | Adverse Effects   | Refs.          |
|---|-------------------------|--|--|---|----------------|
| Clotrimazole                            | Gel/cream               | 3 times/day  | erythematous candidiasis, chronic hyperplastic candidiasis<br>Angular cheilitis                | Occasional effects: skin irritation, burning sensation  | [10,36]        |
|   | Tablets/troches         | 5 times/day  | Intraoral candidiasis  | Occasional effects: skin irritation, burning sensation  | [10,36]        |
| Betamethasone dipropionate clotrimazole | Cream                   | 4 times/day  | Chronic angular cheilitis  | Local irritation  | [10,40–42]     |
| Itraconazole                            | Capsules                | 100–200 mg/day   | Pseudomembranous candidiasis, acute erythematous candidiasis, chronic hyperplastic candidiasis | Nausea, vomiting, diarrhea, abdominal pain  | [36,37]        |
| Voriconazole                            | Infusion                | First day: 6 mg/kg once every 12 h<br>Rest of the treatment: 4 mg/kg once every 12 h                                 | Intraoral candidiasis  | Neuropsychiatric and gastrointestinal effects   | [37,40,43, 44] |
|   | Tablets                 | First day: 200–400 mg once every 12 h<br>Rest of the treatment: 100–200 mg once every 12 h                           | Intraoral candidiasis  | Neuropsychiatric and gastrointestinal effects   | [37,40,43, 44] |
| Posaconazole                            | Oral suspension/Tablets | First week: 200 mg, 4 times/day<br>Rest of the treatment: 400 mg, 2 times/day<br>First day: 3 mg/kg/day (max 200 mg) | Oropharyngeal candidiasis  | Headaches, gastrointestinal effects   | [37,40,45]     |
| Anidulafungin                           | Infusion                | Rest of the treatment: 1.5 mg/kg/day (max 100 mg)<br>First day: 70 mg/day  | Invasive candidiasis   | Occasional effects: anemia, diarrhea, pyrexia, vomiting, hypokalemia  | [19,46,47]     |
| Caspofungin                             | Infusion                | Rest of the treatment: 50 mg/day   | Invasive candidiasis   | Occasional effects: phlebitis, fever, abdominal pain, nausea, diarrhea, headache, rash, leukopenia, hypokalemia | [19,47]        |
| Micafungin                              | Infusion                | 1–2 mg/kg/day (max 100 mg/day)   | Invasive candidiasis   | Occasional effects: fever, nausea, headache, rash   | [19,47]        |

Conventional local oral delivery formulations usually exhibit an initial burst release that rapidly decreases to subtherapeutic concentrations [8], whereas regular antifungal systemic drugs result in severe side effects [48]. Therefore, novel treatment options must be considered for improving anti-*Candida* medicine efficiency while protecting the organism from potentially harmful effects.

An alternative to medication is the use of antiseptic mouthwashes for preventing oral candidiasis development [49]. Their inclusion in oral hygiene practices helps avoid excessive colonization of fungal pathogens and delay *Candida* biofilm formation. Particularly, mouthwashes containing cetyl pyridinium chloride or chlorhexidine were shown effective against both planktonic and biofilm embedded fungal cells [50].

#### 4. Novel Treatment Options

As oral candidiasis' current treatment is becoming rather ineffective due to the emergence of resistant strains, there is an increased research interest towards novel treatment options. The investigated strategies include the use of intrinsic anti-*Candida* materials, antimicrobial nanoparticles, and natural antifungal essential oils and extracts, replacing traditional prosthesis materials and denture adhesives with biomaterials capable of preventing biofilm formation, including regular antifungal agents into targeted and controlled release delivery systems, and combined approaches towards developing the optimum treatment [3,4,48,51–53] (Figure 4).



**Figure 4.** Schematic representation of different biomaterial strategies to combat surface-associated *Candida* biofilms. Reproduced from [21], Frontiers in Microbiology, 2020

##### 4.1. Intrinsic Anti-*Candida* Biomaterials/Compounds

Several materials inherently have antifungal properties that can be exploited in developing superior treatments for oral candidiasis. In this respect, polymeric materials, inorganic nanoparticles, and natural products with intrinsic anti-*Candida* activity are further discussed.

##### 4.1.1. Polymeric Materials

Chitosan is a natural polymer possessing several beneficial properties, such as biodegradability, biocompatibility, fungicidal, antimicrobial, and antitumor activities [54–



57]. It is considered a promising component of mouthwashes and denture adhesives for preventing oral candidiasis [55]. Moreover, low-molecular-weight chitosan solution can be effectively used as an antifungal denture cleanser, showing a significant reduction in *C. albicans* viability in biofilms formed on polymethyl methacrylate [58]. Recently, Ikono et al. [59] examined chitosan nanoparticles of 20–30 nm in diameter for their ability to inhibit *C. albicans* biofilm growth following initial cell attachment. After 3 h of incubation, a greater than 50% reduction in biofilm mass was reported, concluding that chitosan nanoparticles possessed inherent antibiofilm activity but could not entirely inhibit or disrupt *Candida* biofilms [21].

Nylon-3 polymers have been proven to have significant activity against pathogenic strains of *C. albicans* that are resistant to conventional medication. Particularly, nylon-3 polymers with  $\beta$ -amino residues ( $\beta$ NM) in their backbone structure attracted more interest due to their resemblance to proteins that induce biocompatibility [60–63]. Moreover, such nylon-3 polymers can be easily prepared, being promising as clinical antifungal agents [60]. Liu et al. [60] have reported that poly- $\beta$ NM with 20-mer average length displayed strong and selective activity against *C. albicans* strain K1, while only very little hemolysis or toxicity toward 3T3 fibroblasts was detected. Rank et al. [62] have also researched the antifungal activity of nylon-3 polymers. They have evaluated the action of a host defense peptide-like nylon-3 copolymer, obtaining efficacy levels comparable to those of amphotericin B and fluconazole, displaying only mild to moderate toxicity toward mammalian cells.

Guanidines are another class of cationic polymers that can be used as antiseptics and antimicrobials. Particularly, polyhexamethylene guanidine hydrochloride (PHMGH) was evaluated for its antifungal properties [61,64–66]. Choi et al. [67] reported a more potent antifungal activity of PHMGH than amphotericin B, with no hemolytic and lactate dehydrogenase release activities. The researchers also investigated the mechanism of action against *C. albicans*, proving that PHMGH exerts its fungicidal effect by forming pores in the cell membrane. Martini Garcia et al. [64] tested an aqueous solution containing PHMGH against mature *Candida* biofilms formed on denture liner specimens. They registered a total fungal elimination after 10 min of contact without affecting the mechanical properties of the denture liners.

#### 4.1.2. Inorganic Nanoparticles

Silver nanoparticles (AgNPs) are some of the most studied inorganic nanoparticles, being widely utilized for their antimicrobial activity [68,69]. Due to their unique physicochemical properties, beneficial interactions with living structures, and nontoxicity for healthy human tissues, AgNPs may represent key components in developing novel biomedical strategies [21,70–77]. Researchers have reported considerable antifungal activity against *Candida* spp., with potent antibiofilm and cell disruption ability [13,27,78–80]. Monteiro et al. [81] indicated that AgNPs could be used in the treatment of denture stomatitis. The researchers noticed a higher antifungal activity against *C. glabrata* than against *C. albicans*, and more effective action in inhibiting *Candida* biofilm formation than in controlling mature biofilms.

Selenium nanoparticles (SeNPs) have recently gained attention for their antimicrobial properties [21,82]. Shakibaie et al. [83] have demonstrated the anti-*Candida* effects of nanoscale biogenic elemental Se, stating that the mechanism of action requires additional investigation. Guisbiers et al. [84] have synthesized pure SeNPs that successfully inhibited *C. albicans* biofilm formation by adhering to the biofilm, penetrating into the pathogen, and consequently damaging the cell structure by substituting sulfur with selenium. These nanoparticles were able to reduce by 50% the fungal burden in mature biofilms at a concentration of only 25 ppm.

Several nanoscale metal oxides have also been observed to have antifungal properties. Nanoparticles of iron oxide [85–88], zinc oxide [89–93], magnesium oxide [93–96], calcium oxide [94,97], copper oxide [98–100], titanium dioxide [101–104], bismuth oxide



[105,106], and silver oxide [107] display fungistatic and/or fungicidal activities that are useful in the treatment and prevention of oral candidiasis.

#### 4.1.3. Natural Products

Natural products represent a great source of various useful chemical compounds that can be included in diverse biomedical applications [108]. Recently, there is an increased interest in using natural essential oils and extracts as a safer and more efficient alternative to classic antifungal drugs [18,109,110].

Basil extracts have potential use against *Candida* spp. [111,112]. Roozbehani et al. [18] evaluated the effect of basil extracts on *C. albicans* and *C. dubliniensis* adhesion to acrylic surfaces of removable orthodontic appliances. The researchers concluded that such extracts could inhibit the growth, adherence, and formation of biofilms, having great potential as antifungal solutions or mouthwashes.

*Equisetum giganteum*, popularly known as ‘horsetail’ is another plant of antifungal importance [113–115]. Martins Almeida et al. [116] have incorporated *E. giganteum* hydroethanolic extracts into denture adhesives, interfering in the development of *C. albicans* biofilm. This plant extract significantly minimized pathogen colonization and reduced its metabolism, being a promising solution for treating and preventing denture stomatitis.

*Coriandrum sativum* essential oil has also been shown to have inhibitory effects on *Candida* spp., acting similarly to nystatin and amphotericin B [110,117,118]. The results obtained by Furletti et al. [119] indicate the potential use of crude *C. sativum* oil in the prevention and treatment of oral candidiasis, as it demonstrated strong activity against both *Candida* spp. planktonic cells and *C. albicans* biofilm.

Curcumin is an important compound that can be extracted from turmeric [120]. Its antifungal activity is exhibited through various mechanisms, such as targeting metabolic paths, inducing apoptosis, and increasing reactive oxygen species. These properties of curcumin are effective in the design of drug formulations with fewer side effects and superior performance [53,121–124]. Narayanan et al. [125] have evaluated curcumin’s inhibitory action against *C. albicans*, *C. parapsilosis*, *C. glabrata*, and *C. dubliniensis*, proving its potential as a therapeutic alternative to conventional antifungals.

Cinnamon essential oils, cinnamon extracts, and pure compounds also show significant antimicrobial activities against oral pathogens [126]. The antifungal properties of cinnamon are more pronounced than its antibacterial activity, indicating potential use in candidiasis treatments either as the main or a complementary agent [127–130]. De Araujo et al. [131] analyzed the efficacy of mouthwash and spray containing essential oil of *Cinnamomum zeylanicum* Blume for the treatment of oral candidiasis. A mycological analysis demonstrated a reduction of 61% and 33% of *Candida* spp., isolated from oral mucosa and dentures, respectively. *C. tropicalis* elimination was reported in both sites.

Propolis is another natural product presenting anti-*Candida* activity [9]. Ota et al. [132] performed an in vivo study on patients with full dentures who used a hydroalcoholic extract of propolis as a mouth-rinse. The researchers studied the antifungal activity of propolis by sensitivity tests on 80 strains of *Candida* yeasts (20 strains of *C. albicans*, 20 strains of *C. tropicalis*, 20 strains of *C. krusei*, and 15 strains of *C. guilliermondii*). A clear antifungal activity was reported, with the order of sensitivity *C. albicans* > *C. tropicalis* > *C. krusei* > *C. guilliermondii*. Siquiera et al. [9] have also reported the susceptibility to red propolis alcoholic extract of *C. albicans*, *C. tropicalis*, and *C. glabrata* isolated from chronic periodontitis cases.

*Camellia sinensis* and *Hypericum havvae* possess exceptional anti-*Candida* properties and can be used for developing alternative antifungal medication. *Camellia sinensis* has been shown effective against *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. glabrata*, while *Hypericum havvae* is a promising agent against *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. guilliermondii*, and *C. tropicalis* [133].

#### 4.2. Biomaterials for Oral Prosthesis and Denture Adhesives

*Candida* spp. have been shown to form biofilms on the surface of various medical devices made of PMMA, silicone elastomer, polyurethane, polyvinyl chloride, polypropylene, and polystyrene, among others [27]. Additionally, the use of denture adhesives, besides their functional and psychological advantages, has been reported to predispose wearers to oral candidiasis [134]. Hence, these two elements could hold great improvement potential in synergy with fungicidal or fungistatic materials [135].

By coating or functionalizing currently used materials, the oral prosthesis can inherit antifungal properties. As PMMA is one of the most commonly used polymers for fabricating a broad range of dental appliances, most of the studies found in the literature focus on enhancing this material's biocompatibility and functionality [27,48,136–141].

Jung et al. [20] have reported a novel fungal repelling multilayer coating for PMMA-based denture materials. The researchers created an alternating structure through layer-by-layer (LBL) self-assembly. Specifically, amphiphilic quaternary ammonium chitosan was employed as the positive antimicrobial layer, whereas sodium alginate was used as the negative layer to create LBL multilayers on the substrate material. The final composite material was shown to be biocompatible toward mammalian cells and resist under shaking and repeated brushing, indicating a novel long-term strategy in controlling fungal biofilms formation on denture biomaterials.

Different attempts have been made aiming to modify and improve the mechanical properties of PMMA by incorporating various metal oxide fillers and fibers [139]. For instance, studies have proven that adding zirconia nanoparticles (ZrO<sub>2</sub> NPs) to PMMA denture base increases the density and reduces porosity, leading to enhanced flexural strength, tensile strength, and fracture toughness [48]. Moreover, Gad et al. [142] have demonstrated that the addition of ZrO<sub>2</sub> NPs to cold-cured acrylic resin reduces *Candida* adhesion due to its denser and less porous lattice. Gowri et al. [143] have attributed the inhibitory activity of ZrO<sub>2</sub> NPs against fungal strains to their interference in cell function and resulting deformation in fungal hyphae. Hence, these nanoparticles could be included in the material for repairing denture bases and in the PMMA removable prostheses as a possible strategy for preventing denture stomatitis.

Mahmudi et al. [144] proposed the addition of nano-zirconia into the denture adhesive instead of the base material. The researchers observed *C. albicans* growth inhibition at concentrations higher than 31 µg/mL. Therefore, ZrO<sub>2</sub> NPs can be added to the denture adhesives to reduce the possible occurrence and reduce the incidence of *C. albicans*. However, the formulation is effective for prevention purposes only, as it did not cause pathogens death. Alternatively, Namangkalakul et al. [22] stated that high-molecular-weight water-soluble chitosan can serve as an antifungal adhesive to prevent and treat denture stomatitis. Besides, denture adhesives could be used as delivery systems for antifungal agents without affecting their adhesion capacity [134].

A significant reduction of *C. albicans* adherence was also noticed in PMMA imbedded with spherical Ag NPs. Acosta-Torres et al. [140] have evaluated the flexural properties of PMMA-Ag NPs material, showing that they fit within standard required values. Moreover, the obtained biomaterial can be used as a biocompatible antifungal PMMA denture base material that does not affect metabolism and proliferation and does not cause genotoxic damage to cells. A similar strategy was approached by Nam et al. [145]. When combined with Ag NPs at 20 wt %, the researchers reported that the resin displayed antifungal activity while maintaining appropriate physical properties. Nonetheless, it was concluded that color stability must be improved for clinical use.

PMMA behavior can also be improved by the addition of zinc oxide nanoparticles (ZnO NPs). In this respect, Cierech et al. [138] have reported a four-fold higher inhibitory activity on *C. albicans* growth for a 7.5% concentration of ZnO NPs, evaluating the efficacy of nanocomposites PMMA-ZnO-NPs and sputtered ZnO nanoparticles on the PMMA layer. The mechanism through which the antifungal effect is exerted is not completely understood, but it is supposed to happen due to increased concentration of intracellular

singlet oxygen, leading to oxidative stress. Kamonkhantikul et al. [141] have also made use of ZnO NPs. The researchers evaluated antifungal, optical, and mechanical properties of heat-cured PMMA incorporated with various amounts of ZnO NPs with or without methacryloxypropyltrimethoxysilane modification. At the same concentration of ZnO NPs, silanized groups resulted in a greater reduction in *C. albicans* than the non-silanized ones. The best outcomes were reported for PMMA incorporated with 2.5% silanized ZnO NPs, which showed greater antifungal activity, less color difference, and opacity than non-silanized nanoparticles while preserving the mechanical properties of the base material.

Another interesting approach to modifying PMMA is to reinforce this polymer with nanodiamond (ND). Mangal et al. [139] have reported significant improvement in the mechanical properties of PMMA with the incorporation of as little as 0.1 wt % ND resulting in a more than 20% increase in flexural strength over unmodified PMMA. Moreover, the researchers observed pronounced resistance to *C. albicans* and a significant reduction in the formation of salivary biofilm.

#### 4.3. Drug Delivery Systems

As several commonly used antifungal drugs present limited water solubility, poor oral bioavailability, and limited formulation approaches, there is a strong need to develop innovative drug delivery systems [146].

For the treatment of oral candidiasis, sustained drug release is required so that the medication is retained in the oral cavity and produces an antifungal effect for a prolonged time [8]. One patient-friendly option is to elute drugs from biomaterials in order to treat and prevent the fungal infections associated with the use of dental prostheses [27]. In this regard, nanofiber-based scaffolds have recently become popular due to their remarkable properties such as low density, large specific surface areas, high porosity, and very small pore sizes [8].

Another promising possibility is to use nanoparticles for drug delivery, as they improve the biopharmaceutical and pharmacokinetic properties of antifungal agents. These characteristics are further reflected in a greater pharmacodynamic potential, lower toxicity, and prolonged action [147]. In particular, polymeric nanoparticles are attractive due to their two-fold role: drug nanocarrier and intrinsic antimicrobial agent [52]. As reported in the literature, biodegradable polymers such as poly-lactic-glycolic acid (PLGA), chitosan, and liposomes promote a slow, sustained drug release, thus diminishing the medicine dosage and its associated toxicity. Hence, adverse effects are reduced without compromising the therapeutic fungicidal action [15].

Lipid-based nanoparticles are also promising moieties for penetrating the biofilm matrix and targeting fungal cells [21]. Al-Maghribi et al. [148] have successfully encapsulated miconazole into solid lipid nanoparticles (SLNs). According to the researchers, the susceptibility of *C. albicans* to miconazole-loaded SLNs using a well-diffusion technique indicated that the antifungal activity was enhanced when incorporated into the SLNs. Similarly, lipid-based formulations of amphotericin B showed a significant decrease in side effects (i.e., nephrotoxicity) while preserving its broad-spectrum antifungal activity [146].

#### 4.4. Combined Approaches

Regardless of their individual efficacy, the above presented biomedical strategies work best in synergy. In this regard, several researchers have investigated combined approaches between them or studied the effects of novel treatment options in association with classic antifungal drugs.

Karlsson et al. [135] have reported the fabrication of multilayered polyelectrolyte thin films (PEMs) that promote the surface-mediated release of an antifungal beta-peptide. Specifically, the researchers have incorporated a fluorescently labeled antifungal beta-

peptide into the structures of PEMs fabricated from poly-L-glutamic acid and poly-L-lysine manufactured through a layer-by-layer process. The obtained materials showed promising ability in inhibiting the growth of *C. albicans* on film-coated surfaces.

Tonglairoum et al. [8] developed clotrimazole (CZ)-loaded microemulsion-containing nanofiber mats. They have successfully fabricated these mats by electrospinning a mixture of different CZ-microemulsion formulations polymer solutions. The researchers reported an initial burst release, followed by a sustained release of CZ. The mats presented remarkable antifungal properties, while the toxicity remained low. Nonetheless, it was concluded that further in vivo studies are required for material evaluation for the treatment of oral candidiasis.

Kong et al. [11] proposed a different approach by designing a bioadhesive hydroxypropyl methylcellulose hydrogel formulation of Histatin-5 for topical application against oral candidiasis. Histatin-5 was chosen due to its potency in killing *C. albicans*, without inducing resistance. The topical delivery through bioadhesive hydrogels is considered ideal as it provides extended release of the therapeutic agents, a desired characteristic for treating infections. Taking also into account the lack of toxicity, anti-inflammatory, and wound-healing properties of histatin-5, the findings of this study confirm the usefulness and commercial feasibility of this therapeutic strategy.

Another approach is offered by Nagrah et al. [149], who attempted to repurpose PMMA for 3D printing along with functionalization of the tissue surface using the controlled release of polycaprolactone (PCL) microspheres loaded with amphotericin B. The researchers obtained promising results as the 3D printed dentures presented comparable mechanical properties to conventionally fabricated ones, while the PCL-PMMA surface released the drug over sustained periods, actively reducing *C. albicans* colonization in a biomass assay.

Tejada et al. [26] mixed gelatin (GEL) and chitosan (CH) in various ratios to create natural polymeric blend-based nanoparticles aimed to deliver miconazole nitrate and lidocaine chlorohydrate. A faster release was observed when the GEL/CH ratio was higher, possibly due to GEL solubilization in the medium that led to the erosion of the polymer matrix and release of encapsulated drugs. Nanoparticle-encapsulation conducted to a sustained release for 24 h, indicating the potential of such systems to be included in a buccal film or a buccal tablet to obtain an alternative therapeutic formulation for the treatment of *C. albicans*.

## 5. Conclusions

To summarize, oral candidiasis can be a life-threatening infection for immunocompromised individuals, requiring strong antifungal drugs. The classic therapeutic approach implies the administration of different polyenes, azoles, or echinocandins, while prevention is ensured through good hygiene practices and attention to proper denture fit. To avoid *Candida* spp. overgrowth and limit the adverse effects associated to traditional antifungal agents, advances have been made for developing anti-*Candida* biomaterials.

By making use of inherently fungistatic or fungicidal polymeric, inorganic, and natural products, several strategies can be developed to prevent and fight these oral infections. Coating, functionalizing, and/or incorporating them into denture base materials are all considered efficient novel treatment options for oral candidiasis. Besides, delivering classic drugs via controlled delivery systems helps reducing adverse effect without hampering the therapeutic performance. Nonetheless, the alternatives combining several biomaterials approaches have been proven remarkably successful.

Therefore, the current and underdevelopment treatment options presented in this review can stand as inception points for further research. Considering the characteristics of each of the previously described compounds, biomaterials, and delivery methods, better oral hygiene products, prosthesis materials, denture adhesives, and therapeutic formulations can be created.

To conclude, there is an increased research interest towards developing innovative *Candida*-inhibiting biomaterials. However, despite the significant progress that has been made towards finding better oral candidiasis treatment strategies, there is still room for improvement. Particularly, most of the tested compounds and biomaterials have not yet advanced beyond preclinical testing, and special attention must also be given to currently understudied complex and mixed biofilms.

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