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REVIEW ARTICLE

Promising Alternative Therapeutics for Oral Candidiasis

Célia F. Rodrigues[1,2], Maria E. Rodrigues[1] and Mariana C.R. Henriques[1,*]

[1]*CEB, Centre of Biological Engineering, LIBRO - Laboratorio de Investigacao em Biofilmes Rosario Oliveira, University of Minho, 4710-057 Braga, Portugal;* [2]*LEPABE, Department of Chemical Engineering, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, s/n, 4200-465 Porto, Portugal*

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Abstract: *Candida* is the main human fungal pathogen causing infections (candidiasis), mostly in the elderly and immunocompromised hosts. Even though *Candida* spp. is a member of the oral microbiota in symbiosis, in some circumstances, it can cause microbial imbalance leading to dysbiosis, resulting in oral diseases. Alternative therapies are urgently needed to treat oral candidiasis (usually associated to biofilms), as several antifungal drugs' activity has been compromised. This has occurred especially due to an increasing occurrence of drug-resistant in *Candida* spp. strains. The overuse of antifungal medications, systemic toxicity, cross-reactivity with other drugs and a presently low number of drug molecules with antifungal activity, have contributed to important clinical limitations.

We undertook a structured search of bibliographic databases (PubMed Central, Elsevier's ScienceDirect, SCOPUS and Springer's SpringerLink) for peer-reviewed research literature using a focused review in the areas of alternatives to manage oral candidiasis. The keywords used were "candidiasis", "oral candidiasis", "biofilm + candida", "alternative treatment", "combination therapy + candida" and the reports from the last 10 to 15 years were considered for this review.

This review identified several promising new approaches in the treatment of oral candidiasis: combination anti-*Candida* therapies, denture cleansers, mouth rinses as alternatives for disrupting candidal biofilms, natural compounds (*e.g.* honey, probiotics, plant extracts and essential oils) and photodynamic therapy.

The findings of this review confirm the importance and the urgency of the development of efficacious therapies for oral candidal infections.

Keywords: *Candida*, oral candidiasis, resistance, antifungal treatment, plants, honey, probiotics, photodynamic therapy.

1. INTRODUCTION

In the last decades, the incidence of human fungal infections [1] has increased significantly. This RISE has been mostly attributed to the widespread provision of new medical practices, such as immunosuppressive therapy and the use of broad-spectrum antibiotics, and to invasive surgical procedures such as solid organ or bone marrow transplantation [1]. Of the fungi involved in human infections, members of the *Candida* genus are amongst the most prevalent, which are particularly associated with superficial infections, affecting moist mucosal membranes, as the oral cavity [2]. Indeed, *Candida* spp. are frequently found in the mouth of healthy individuals and, as such, this microorganism is considered a member of the normal oral microbiome [3]. In healthy individuals, the oral cavity is a balanced, albeit complex, environment where a rich microbiome (bacteria, virus, and fungi) cohabits with a diversity of coexisting surfaces, *i.e.* teeth, gingival sulcus, tongue, cheeks, and hard and soft palates. However, shifts in this environment, as in pH and sugar concentrations, or the use of oral prosthetic devices or implants, disrupt the balanced state and lead to the development of infections and disease [4]. In these conditions, the species

*Address correspondence to this author at CEB, Centre of Biological Engineering, LIBRO - Laboratorio de Investigacao em Biofilmes Rosario Oliveira, University of Minho, 4710-057 Braga, Portugal; E-mail: mcrh@deb.uminho.pt

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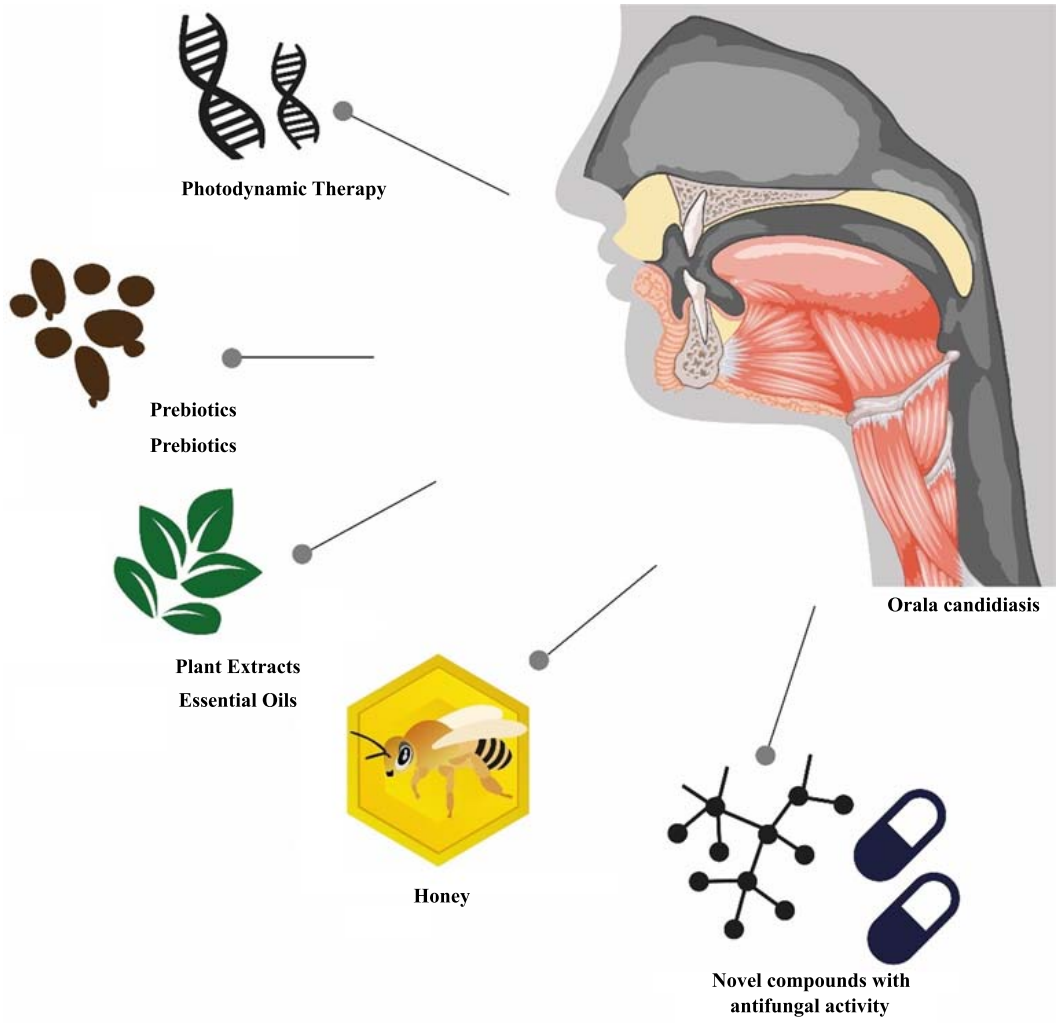

Fig. (1). Alternative therapeutics to treat oral candidiasis.

composing the oral microbiome, including *Candida* spp., may become causative agents of disease. Indeed, oral candidiasis occurs frequently in oral cancer, burning mouth syndrome, taste disorders and previous endocarditis [3].

Oral candidiasis has been described throughout human history, since the times of Hippocrates (460-370 bC), being referred to as 'a disease of the diseased', reflecting the opportunistic pathogenic nature of *Candida* spp. [3]. Among more than 350 heterogeneous species of *Candida* spp., *Candida albicans* is the most prevalent in human oral candidiasis [5]. However, the non-*albicans Candida* (NAC) spp. are progressively encountered and recognized as important agents of human oral infections [3, 5-9]. The increased involvement of NAC spp. in oral candidiasis has been attributed to improvements in diagnostic methods, which can now more accurately differentiate these species from *C. albicans* [10]. Still, the increase may also reflect the inherently higher level of antifungal drug resistance in some NAC spp. [11] compared to *C. albicans*, as this would promote their persistence in mixed-species infections treated with traditional antifungal agents [3,4].

For both *C. albicans* and NAC spp., the transition from a harmless commensal to a pathogen is complex and poorly understood, but appears to involve an altered expression of virulence factors [3]. One of the most relevant virulence factors identified so far for *Candida* spp. is their ability to form biofilms [12]. These can play an important role in clinical oral infections because of their resilience and resistance to normal host removal mechanisms and also to antimicrobial therapy [13, 14]. The involvement of *Candida* spp. biofilms in human oral infections is well documented, particularly when occurring in the presence of oral prosthesis, usually as a consequence of poor oral hygiene [2, 4]. Also, in the event of host debilitation, which causes an ecological shift in favor of yeasts' growth, *Candida* spp. biofilms may develop on the mucosa itself [14, 15]. Oral biofilms are particularly diffi-

cult to eradicate due to their complex structure and recalcitrance. Disinfection of the oral cavity and the use of antifungal agents are important for managing the infection, but the increased resistance of *Candida* spp. (especially in biofilm form) to these conventional agents [16, 17] requires the development of alternative solutions [2, 4, 18]. Although the mechanisms of biofilm resistance to antifungal agents are not fully understood, the current consensus is that biofilm resistance to drugs is a complex multifactorial phenomenon involving molecular mechanisms different from those displayed by planktonic cells [4, 12]. Strategies of inhibition of the biofilm may represent a new paradigm for antifungal discovery, and should ideally be able to efficiently prevent the development of the biofilm in the first instance, and eradicate established biofilms [2].

In this review, alternatives to the present treatments of oral candidiasis will be presented and discussed (Fig. **1**).

2. ORAL CANDIDIASIS: ALTERNATIVES TO THE ACTUAL ANTIFUNGAL TREATMENTS

The prevalence of oral candidiasis continues to increase and is one of the most common and major healthcare challenge [2-4]. The presence of candidal biofilms reduces the possibility of removal of organisms by the host defense mechanism and by antifungal drugs. From a clinical viewpoint, the most important feature of *Candida* spp. biofilms is, indeed, their role in resistance to conventional antifungal therapy [16]. Several research groups have confirmed that *Candida* spp. cells present in oral biofilms have high levels of resistance to the most commonly used antiseptics or antifungal agents [4, 17].

Taking into consideration the increasing number of *Candida* spp. oral strains with elevated drug resistance, the identification of effective alternative therapies to the current antifungal agents is essential. Many approaches are presently being followed and evaluated, comprising the photodynamic therapy, natural approaches, the exploitation of the antifungal properties of plant derivatives and honey and the investigation of novel compounds with antifungal activity. An outline of the latest advances in these approaches is provided in the next sections.

2.1. Photodynamic Therapy

The use of photodynamic therapy (PDT) to fight fungi infections has been showing promising results in the treatment of candidiasis [19]. In this method, a photosensitive substance (nontoxic dye) is activated by a light source of a specific and appropriate wavelength. The activation of photosensitizers, in the presence of oxygen, promotes a phototoxic response on the cells, usually by oxidative damage [20], which leads to disorganization of the cell wall as well as DNA damage, thus causing cell death [21, 22]. The PDT sensitization depends on the time of incubation and type of photosensitizer, time of exposure and energy density of the laser concentration of photosensitizer and the physiological state of the microorganisms [21, 23]. Different photosensitizers, both natural and synthetic, mostly belonging to the phenothiazine dyes, have been explored for their utility as antifungals in PDT. Methylene blue, new methylene blue and toluidine blue have shown effectiveness in the reduction of fungi. Malachite green, a cationic dye of the triarylmethane family is also a possible choice [19, 21-26].

Sousa and colleagues [23] evaluated the *in vitro* effect of laser radiation and/or with methylene blue in several *Candida* spp. Methylene blue and laser radiation reduced the number of cells count for *C. albicans* (88.6%), for *C. dubliniensis* (84.8%), for *C. krusei* (91.6%) and for *C. tropicalis* (82.3%). By contrary, laser radiation or methylene blue did not decrease significantly the number of cells count on *Candida* spp. Samples alone, except for *C. tropicalis*. In another PDT study, the combination of methylene blue with potassium iodide also demonstrated to improve *in vitro* biofilm cell reduction, by practically eradicating a *Candida* spp. infection in an *in vivo* oral model [19]. Dovigo *et al.* [27] reported that a second generation photosensitizer - Photodithazine® and a light emitting diode (LED) light promoted a significant decrease in the viability of oral clinical isolates of *C. albicans*, *C. glabrata* and *C. tropicalis* isolates. Recently, the same combination proved to be as effective as nystatin against oral candidiasis in mice [25]. This result seems to be promising, since polyenes - as nystatin - still have a good *Candida* spp. antifungal activity [12]. PDT has also been studied to be used as a prophylactic method for oral candidiasis. Soares *et al.* [26] assessed the influence of toluidine blue O and LED irradiation on the growth and adhesion of *C. albicans*, *C. tropicalis*, and *C. parapsilosis* isolates to buccal epithelial cells. They concluded that the PDT inhibited the adhesion (in 55%) of the *Candida* spp. to buccal epithelial cells. As the adhesion of *Candida* spp. to host cells is an essential step for the biofilm formation, colonization and infection, any method that inhibits candidal adhesion may have a great potential to be used in therapy. Although photodynamic protocols are optimized for the treatment of specific cutaneous infections, there is still limited

information about its mechanism of action, as well as the risks to healthy tissues [28].

The application of non-specific oxidizing agents in the PDT procedures to eliminate organisms with resistance to conventional antifungal agents may be therapeutically interesting. Importantly, the development of resistance to this therapy seems unlikely, making this a very promising therapy for combating pathogens as *Candida* spp. [20]. Nonetheless, it seems to be important to address more studies with *C. glabrata* strains, since this species has been reported as less sensitive to PDT. Other species -*Candida parapsilosis* and the most recent (and extremely drug resistant) *Candida auris* - also require evaluation.

2.2. Natural Approaches

2.2.1. Probiotics and Prebiotics

Probiotics are alive microorganisms that provide health benefits for the hosts when administered/consumed in the adequate amounts [29, 30]. *Lactobacillus* and *Bifidobacterium* genus are still the most commonly used [30]. Initially, probiotics, which are mainly lactic acid bacteria, were thought only to be used for managing the intestinal microbiota (*e.g.* diarrhoea, inflammatory bowel and lactose intolerance complications), but further studies indicated broad health benefits, such as general immunostimulation (defence), acid and bile tolerances, antagonistic activity against pathogens in respiratory or urinary tracts [30-32]. To be seen as safe for human consumption, the probiotics, are required to be of human origin, and cannot transmit any antibiotic resistance genes [30].

These microorganisms have been reported as good prophylactic and therapeutic alternative agents for the management of oral candidiasis [33-41]. Most of the oral health studies with probiotics have been concentrated specifically in dental caries and periodontitis [42-46]. The exact mechanisms of action of probiotics against *Candida* spp. are still unclear, but it is thought that the restoration of a natural healthy microbiome is responsible for its anti-*Candida* spp. activity [30]. The microbiome restoration is thought to lead to five phenomena that contribute to this activity: co-aggregation of probiotic and fungal cells to inhibit fungal colonization; production of antimicrobial and anti-biofilm compounds; competition for available nutrients and adhesion sites; production of *quorum sensing* chemicals that lead to down-regulation of toxin production by the fungi; modulation of the humoral and cellular immune system of the host [36,47]. In general, studies have validated that the administration of single or multiple strains of probiotic bacteria, alone or in combination with antifungal drugs is able to reduce the *Candida* spp. colonization, improve the antifungal activity and relieve signs and symptoms of candidiasis [47]. Probiotic antimicrobial substances which directly increase the inhibition of yeast forms of *Candida* spp. include organic acids (*e.g.* lactic acid, acetic acid), and bacteriocins (*e.g.* bacteriocin L23 [48], plantaricin [49] and pentocin TV35b [50]) [51]. Other molecules with a significant anti-*Candida* spp. effect include hydrogen peroxide, lactic acid (produced by lactobacilli), and low molecular weight compounds (*e.g.* reuterin [52], reutericyclin [53] and dyacetyl [54]) with an anti-*Candida* spp. effect in the yeast forms [55, 56].

Hayama *et al.* [57] reported that *Lactobacillus pentosus* S-PT84 inhibited mycelial growth of *C. albicans* TIMM1768 *in vitro*, and protected the host from *C. albicans* infection, reducing lesional scores on tongues *in vivo*, thus demonstrating a prophylactic effect against oral candidiasis in mice. On the other hand, regarding the *in vivo* animal studies, the results remain controversial. Some works suggest a local and a systemic beneficial effect of probiotics on oral and systemic candidiasis [58-60], whereas others indicate inconclusive effects [61]. These dissimilarities may be result from variances in the administration technique employed, but also the probiotic species involved. Matsubara *et al.* [60] indicated that the effects of probiotics may be better than the antifungals' in decreasing oral candidiasis. They also found that the capacity of probiotics in combating *Candida* spp. biofilms is both species and strain-specific [62, 63]. The selection of the appropriate strain(s) of probiotic(s) for therapeutic purposes needs to be prudently performed and seems to be a key factor for the effectiveness of probiotics against *Candida* spp. oral infections [62, 63]. It is documented that the high variation of the genome size of *Lactobacillus* (1.23-4.91 Mb) and the GC content (31.9-57.0%) [64] confer to this genus diverse properties [65, 66] and specific strains have been related to favorable effects on *Candida* spp. oral infections [46]. James and colleagues [67] published results in the evaluation of selection and combinations of *Lactobacillus*: *Lactobacillus plantarum* SD5870, *Lactobacillus helveticus* CBS N116411 and *Streptococcus salivarius* DSM 14685. They have demonstrated that the co-incubation with probiotic supernatants or live probiotics under hyphae-inducing conditions decreased *C. albicans* biofilm formation and size in all treatment groups. Quantitative real-time polymerase chain reaction (Real-Time PCR) exposed that the combined supernatants significantly reduced the expression of sev-

eral *C. albicans* genes involved in the yeast-hyphae transition, biofilm formation, tissue invasion and cellular damage, between 0.99 and 70%. The combination of *L. plantarum* SD5870, *L. helveticus* CBS N116411 and *S. salivarius* DSM 14685 was, thus, considered effective at both preventing the formation of and removing *C. albicans* pre-formed biofilms [67]. Taking into account these results, this probiotic selection could be also interesting for the control of oral infections from other *Candida* spp. which also produce hyphae or pseudohyphae, as *C. tropicalis* or *C. parapsilosis*. Antifungal activity against blastoconidia and *Candida* spp. biofilm inhibition was also described by Song *et al.* [68] when using probiotics (*L. rhamnosus* and *L. casei)* on the denture surfaces. Neither of the probiotics affected the surface roughness of the denture base resin, showing to be the ideal probiotics for the prevention and treatment of denture-related stomatitis. In this case and since it has activity in blastoconidia, the mix *L. rhamnosus* and *L. casei* could also be applied to the inhibition of *C. glabrata* biofilms. In a study with a different probiotic [69], *Bacillus subtilis* R0179, was found to have a significant antifungal effect against oral *Candida* spp., exhibiting clear zones of inhibition for *C. albicans* and *C. parapsilosis* but not for *C. krusei*. A notable reduction in the number of *Candida* spp. cells and abundant *Candida* spp. cell death were visualized microscopically. The authors identified a preliminary antifungal mechanism of *B. subtilis* R0179 and detected an antifungal agent, Iturin A.

The use of probiotics in toothpaste has also been assessed. Amižić *et al.* [70] evaluated the antimicrobial capacity of two probiotic toothpastes containing *Lactobacillus paracasei* and the other *Lactobacillus acidophilus*, comparing to one toothpaste without probiotic, and in a combination with two different mouthrinses (one containing essential oils and the other containing hexitidine). Their results showed that the probiotic toothpastes had a clear, better inhibitory effect than toothpaste without probiotic in the case of *C. albicans* and *S. salivarius*. In all cases, toothpastes had stronger inhibition capacity than mouthrinses ($p \leq 0.05$), and can be used for the prevention of oral infectious diseases [70]. Mishra *et al.* [71] verified parallel effects but in an oral rinse. In their study, a probiotic rinse showed to be equally effective as 0.2% chlorhexidine digluconate rinse in reducing *C. albicans* cells after one week of intervention, but the herbal oral rinse was least effective. Since chlorhexidine has a good antimicrobial activity, the authors' results demonstrate in this report the great advantage in using probiotics for the control of oral candidiasis. Likewise, the use of a rinse with antifungals or antifungals plus probiotics (combination of *Bifidobacterium longum*, *Lactobacillus bulgaricus,* and *Streptococcus thermophilus*) showed that both groups had a significant reduction in general oral candidiasis symptoms [39], but *Candida* spp. reduced significantly more in the probiotic group as compared to the control group. In dentistry, the main objective of endodontics is the avoidance of a periapical infection. The apical periodontitis, in an acute or chronic form, can occur because of the persistence of pathogens as *Enterococcus faecalis* and *C. albicans*, harboured in the root canal systems of the teeth. Bohora and Kokate [72] disclosed that *Lactobacillus* and *Bifidobacterium* inhibit *E. faecalis* growth and no effect was detected on *C. albicans*. Curiously, in the biofilm form, both had an antibacterial effect on pathogenic organisms.

The regular intake of probiotics has also been related to a decrease in the incidence of oral candidiasis. Miyazima and colleagues [73] evaluated the effect of consumption of cheese supplemented with *L. acidophilus* NCFM or *L. rhamnosus* Lr-32, daily for eight weeks on the oral colonization of *Candida* spp. in denture wearers. The authors concluded that a daily consumption of cheese supplemented with probiotics, reduced the colonization of oral *Candida* spp. in complete denture wearers, suggesting a potential reduction in the risk of oral candidiasis in a highly susceptible population. Other authors have found similar results [38, 41]. Interestingly, Oliveira *et al.* [74] showed that when *Candida* spp. cells interacted with *L. rhamnosus,* a significantly lower proteinase, and hemolysin activity was detected when compared with control group. Also, the germ tube formation and biofilm formation capacity have also decreased, with alterations in susceptibility to antifungal drugs. This seems to be important for the inhibition and control of biofilms in hyphae and pseudohyphae *Candida* spp. producers, but also in strains with a high capacity of producing biofilm matrix biopolymers (*e.g.* carbohydrates).

Importantly, Mendonça and collegues [40] demonstrated that probiotic bacteria (*L. casei* and *Bifidobacterium breve*) severely reduces the *Candida* spp. colonization in the oral cavity of the elderly and increases specific secretory immune response against these yeasts (an increase of the anti-Candida IgA levels), thus suggesting its possible use in controlling oral candidiasis. Other authors have stated analogous results in IgA secretory responses [58, 75].

2.2.2. Prebiotics

In 1995, Gibson and Roberfroid [76] defined prebiotics as "a non-digestible food ingredient that benefi-

cially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health". Examples of prebiotics for intestinal lactic acid bacteria are sugars and dietary fibers [76]. Though, since sugars highly increase the risk of dental caries and other oral pathologies, in the oral environment case, this is not valid [46, 77]. Xylitol, a sugar with an alcohol group, is normally not assimilated by lactobacilli. Nevertheless, a recent report indicated that 36% of lactobacilli strains isolated from human oral cavities were able to metabolize xylitol [78] and Kojima and colleague's work showed a decreased growth of *C. albicans* ATCC18804 in the presence of xylitol, xylose, and arabinose when compared with glucose [62]. In a series of clinical trials (Turku sugar studies) Larmas *et al.* [79,80] presented results informing that in the xylitol intake group, a significant decrease in the detection and colony counts of oral *Candida* spp. was observed. Moreover, other authors [81, 82] demonstrated that the presence of xylitol inhibits the adhesion of *Candida* spp. to the oral mucosal surfaces. This highlights the indirect xylitol anti-*Candida* spp. activity (prebiotic activity), through the increased induction of lactobacilli oral community, which used this sugar to increase the number of yeasts cells. Other molecules can be adjuvants in this process and should be further evaluated.

2.2.3. Plant Extracts and Essential Oils

Medicinal plants have been used since pre-historic times for therapeutic purposes and, currently, several works report that the natural compounds are responsible for antimicrobial activity in many fungal pathogens [83-85]. Secondary metabolites such as flavonoids, glycosides, terpenoids, tannins, and alkaloids have been related to these properties [86,87].

The plant extracts composition is variable, depending on the solvent used in the extract preparation [88].

Extracts from *Juglans regia*, *Eucalyptus globulus*, *Pterospartum tridentatum* and *Rubus ulmifolius* were described as effective against oral isolates of several *Candida* spp. [89]. The anti-biofilm forming activity was demonstrated, although the double concentration of extract was generally required to obtain an antifungal effect in biofilm, similarly to that of planktonic cells [90]. The combination of natural compounds with other antifungal drugs to combat *Candida* spp. infections has also been assessed. Kumar *et al.* [91] described a synergistic anti-candidal activity of two asarones (∞ and β) purified from *Acorus calamus* in combination with fluconazole (Flu), clotrimazole, and amphotericin B (AmB), further reducing their minimal inhibitory concentrations necessary to inhibit the biofilm formation of *Candida* spp.. Similar results were demonstrated in a study with a combination of AmB and acteoside, from *Colebrookea oppositifolia* [92].

The essential oils are also composed of an extraordinary mixture of compounds and their hydrophobicity is intimately related to the fungicidal activity [93-96]. That feature is assumed to allow their close interaction with the lipid bilayer of the fungal cell membrane, leading to an amplified permeability, outflow of cell contents and, consequently, to cell death [97]. Antimicrobial activity in *C. glabrata* oral isolates was detected for *Origanum vulgare*, *Lippia graveolens* and *Cinnamomum zeylanicum* essential oils [98]. Promising inhibitory results against some *Candida* spp., particularly *C. tropicalis* and *C. glabrata* were reported when *Glycyrrhiza glabra* extracts were used [90]. Very recently, the anti-*Candida* spp. activity of essential oils from leaves of *Hymenaea courbaril var. courbaril*, *Myroxylon peruiferum*, and *Vismia guianensis* from Brazil was assessed by Costa *et al.* [99]. The oils containing caryophyllene oxide, *trans*-caryophyllene, spathulenol, α-pinene and humulene epoxide II showed antifungal activity against *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, and *C. krusei*, demonstrating to have a good potential for clinical applications in the treatment of oral candidiasis. In a different approach, a study evaluated the capacity of mouth rinses with natural compounds to reduce *C. albicans* biofilms. Souza *et al.* [100] studied the effectiveness of essential oils (EOs) against dental prosthesis infections related to *C. tropicalis*. Among the tested samples, *Pelargonium graveolens* was the most effective oil. Geraniol and linalool were the major constituents and treatments with essential oil, linalool, and geraniol significantly reduced the number of viable biofilm cells and inhibited biofilm formation after exposure for 48 h, with no toxicity associated, showing interesting results in the prevention or treatment of *C. tropicalis* infections. In a 2011 report, Pires *et al.* [101] investigated the anticandidal activity of sixteen essential oils on planktonic and biofilm cultures of *C. parapsilosis* complex. The authors indicated that most active EO was cinnamon oil (CO), which showed anticandidal activity against *C. orthopsilosis* and *C. parapsilosis* in both suspension and biofilm cultures. CO also inhibited biofilm formation (MBIC), but no synergism with amphotericin B was observed. It was concluded that CO is a natural anti-candidal agent that could be effectively utilized for the control of the tested yeasts. Listerine (Pfizer Consumer Health Care, UK) which contains eucalyptol,

thymol, menthol as natural active agents was able to reduce the viability of 48 h *C. albicans* biofilms by approximately 80% [102]. Shino *et al.* [103] also showed that coconut oil has a comparable significant antifungal activity to ketoconazole on *C. albicans*. In another recent study, Saleem *et al.* [104] reported that the polyphenol ichochalcone-A, found in the roots of *Glycyrrhiza* species, reduced the *Candida* spp. biofilm growth, exceeding Flu and no apparent toxicity was detected. Lichochalcone-A was related to the decrease in the proteinases and phospholipase activities, suggesting the potential efficacy as a topical treatment. Further, in a mouse model of oral candidiasis, tongue tissues samples of lichochalcone-A-treated presented with a lesser degree of infiltration and colonization of *C. albicans* compared with the control [104]. Likewise, CO, was found to be the most active out of a range of essential oils, showing candidacidal activity against both planktonic and biofilm cultures of oral clinical isolates *C. albicans*, *C. glabrata*, and *C. krusei* [105].

Although the results in plant extracts and essential oils are encouraging, the antifungal effects reported are mainly related to an inhibition and not to the elimination of the biofilm, which is a huge disadvantage. More studies are needed, in order to improve the activity of the compounds of these mixtures.

2.2.4. Honey

Bactericidal, bacteriostatic, antiviral, anti-inflammatory, antioxidant or anti-tumoral are the therapeutic properties of honey that have been described [106-116], giving this product an extremely important role in the traditional and modern medicine. Nonetheless, few published reports, the available conclusions and the results on the antifungal activity of honey seem favorable.

Very recently, Shokry *et al.* [117] evaluated three honey samples collected from northern (Mazandaran, A), southern (Hormozgan, B) and central (Lorestan, C) regions of Iran and tested them against different pathogenic oral *Candida* spp. isolates. The results showed that all had antifungal activities against Flu-resistant *Candida* spp. *C. krusei* and *C. glabrata* were the two strains with less susceptibility and *C. tropicalis* and *C. albicans* the two with the higher susceptibility to the honey samples [117]. Irish *et al.* [113] examined three floral kinds of honey and one artificial honey (simulating honey's typical high sugar levels) against *C. albicans*, *C. glabrata,* and *C. dubliniensis* clinical isolates. The results showed that *C. dubliniensis* was the most susceptible species to the activity of honey, while *C. glabrata* was the least susceptible. The floral honey types had greater antifungal activities when compared to the artificial honey. Estevinho *et al.* [106] also remarked this observation. In their study, a synthetic honey solution was tested, in order to conclude if the antifungal activity was attributable to sugars. They found that the activity was reduced when compared to the natural honey, thus, it is suggested that the element(s) of honey responsible for the antifungal properties are not sugar based. The source of the honey needs to be optimized to have a greater anti-*Candida* spp. activity. It is, once more, noticed that *C. glabrata* demonstrates to have a higher recalcitrance to the treatment, in comparison to the other evaluated *Candida* spp. Complementing the studies with more *C. glabrata* strains and other less common species to different types of honey sources, the future studies would be interesting, in order to try to understand this effect. Additional *in vitro* and *in vivo* evaluations are still necessary to fully measure the antifungal potential of honey.

2.3. New Compounds with Promising Antifungal Activity

The increase in the resistance to the available antifungal drugs related to *Candida* spp. infections, demands a need in the development of novel and more effective antifungal agents with new targets and new sources (natural or synthetic). Hence, novel molecules are being discovered, synthesized and evaluated for their capacity to control *Candida* spp. growth and, in the future, will be used for the treatment of (recurrent) oral candidiasis. Aldehydes, hydrazones, and hydrazines were assessed against *Candida* spp., with promising results with the activity of these compounds assumed to be on the fungal membrane [118]. Comparably, N-acyldi N-acyldiamines have demonstrated a moderate to good antifungal activity against *C. albicans*, *C. tropicalis*, *C. glabrata* and *C. parapsilosis* [119] and several Mannich base-type eugenol derivatives were also studied against *C. glabrata*, *C. albicans* and *C. krusei*, with good results on inhibitor concentration - IC50 - values, even below those of Flu [120]. On the other side, Vartak and colleagues [121] have recently isolated a new polyene with activity against *C. albicans*, *C. krusei* and *C. glabrata.* Carradori *et al.* [122] synthesized more than a hundred molecules of the 1,3-thiazolidin-4-one nucleus and their N-benzylated derivatives. These compounds showed potential as anti-*Candida* spp. agents, with comparable or even higher biological activity of clotrimazole, ketoconazole, miconazole, tioconazole, Flu, and AmB and with low cy-

totoxic effects. Chemical modifications in glucosides compounds have been performed and their activity against *Candida* spp. has been evaluated by de Souza *et al.* [123]. The authors reported that one of the modified glucosides presented fungistatic activity was threefold higher than Flu, and had a promising fungicidal activity against *C. glabrata*. This compound was considered as a novel structural pattern in the development of new antifungal drugs.

One approach under exploitation is nanotechnology, which allows the design of drugs with extended persistence and controlled release. Perera *et al.* [124] assessed the encapsulation of citric acid into a Mg-Al-layered double hydroxide. The results demonstrated a topical improved antifungal activity against *C. albicans* and *C. glabrata*, but not *C. tropicalis*. Similar results were presented by Silva *et al.* [125] using silver nanoparticles. Additionally, another investigation indicated that silver nanoparticles loaded with AmB can also be a potential new model formulation able to improve the antifungal therapeutic efficiency of AmB against *Candida* spp. [126].

Other tactics have also been arranged. The combination of epigallocatechin gallate (EGCG) with miconazole, Flu or AmB has shown to have a synergistic effect against planktonic and biofilm cells of *Candida* spp. [127]. The authors stated that this combined treatment could lower the dosages of antifungal drugs which are necessary to treat infections, thus preventing possible adverse effects and the emergence of resistant strains. Alternatively, the antifungal effect of helical β-peptide structural mimetics of natural antimicrobial α-peptides was assessed by Raman *et al.* [128], against clinical isolates and drug-resistant *Candida* spp.. *C. tropicalis* was the most susceptible, while *C. glabrata* was the least susceptible. Remarkably, although they were mostly ineffective at disrupting *Candida* spp. biofilms, these compounds could prevent the formation of *C. albicans*, *C. glabrata*, *C. parapsilosis* and *C. tropicalis* biofilms, appearing to be a promising class of molecules to use as therapeutics. Already known antibacterial agents are also being evaluated for their potential antifungal activity. For instance, chloramphenicol antifungal activity was found comparable to caspofungin, ketoconazole, and metronidazole, however, it had no activity against most tested strains of *C. albicans C. famata*, *C. glabrata*, and *C. haemolonei* [129].

In an interesting line of research - defense mutualisms between social insects and microorganisms - have been also studied. It is recognized that the symbiotic nature of endophytic microorganisms leads to metabolic interactions between the host and the environment, and thus the production of bioactive compounds [130]. Reports have described the discovery of three active fungal extracts, resulting in the isolation of eight compounds with antifungal and cytotoxic potential against *C. albicans* ATCC10213 [130]. In 2013, Nirma *et al.* [131] indicated the finding of a *Pseudallescheria boydii* strain isolated from *Nasutitermes sp*. The symbiosis originated the production of two metabolites with antifungal activity against *C. albicans* and *C. parapsilosis*: tyroscherin and N-methyltyroscherin. Two years later, they also revealed new compounds, ilicicolinic acids A, C, and D and ilicicolinal isolated from *Neonectria discophora* SNB-CN63 isolated from a termite nest, with *in vitro* antifungal activity against *C. albicans* and *C. parapsilosis* [132].

All these studies are still preliminary and need to be further explored, but they might be a good source of new antifungal drugs to treat oral candidiasis and have shown to have a broader anti-*Candida* spp. spectrum, than the other discussed alternatives.

CONCLUSION

Candida spp. oral infections are becoming more serious and more recalcitrant to antifungal treatments, especially to azole class drugs. It is, thus, important to search for alternative treatments and to evaluate combinational drug protocols, in order to effectively replace the traditional antifungal regimens.

The photodynamic therapy has been deeply studied and the data to date suggest that the oxidizing photodynamic treatment methods hold great potential for combating oral candidiasis, due to unlikely development of resistance mechanisms in this procedure. On the other side, the use of probiotics and prebiotics also seem to have encouraging results, due to a general induced immunostimulatory effect in the host. Plant extracts, essential oils, and honey have also exhibited valuable antifungal activities. Additionally, new compounds have been discovered in nature (mostly from symbiosis relations), but have also been synthesized entirely in the laboratory, which, in a near future, will allow having new sources of antifungal responses.

Compared with conventional antifungal therapies for oral candidiasis, all these alternative therapies have been proving to improve certain clinical conditions and reduced the prevalence of *Candida* spp. Thus, the novel antifungal appears to be promising in eliminating oral *Candida* spp. biofilms, however, they are yet to be carefully tested in human clinical trials, and the toxicities of many of the compounds are yet to be evalu-

ated to establish the legitimacy of the declared effectiveness

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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