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The potential management of oral candidiasis using anti-biofilm therapies

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ABSTRACT

Candida albicans is a minor component of the oral microbiota and an opportunistic pathogen that takes advantage of the immunocompromised host and causes oral mucositis and oral candidiasis. This organism is able to undergo phenotypic modification from a yeast to hyphae growth phase, one of the key arsenals for immune cell evasion, tissue invasion and biofilm formation. The latter property coupled with overgrowth and immune compromising factors such as HIV/AIDS, cancer treatments, organ transplantation, diabetes, corticosteroid use, dentures, and broad-spectrum antibiotic use have modified the fungus from a normal component of the microflora to a foe of an oral cavity and resulting in reduced sensitivity towards commonly utilised antifungal agents. Hence, the need for alternative therapy to curb this plight is of importance. Making use of biomolecules produced by *Streptococcus mutans*, application of lactoferrin which is a nonspecific host defense factor found in saliva with metal chelating and broader antimicrobial properties, use of probiotics which have the capacity to boost the host immunity through eliciting Immunoglobulin A synthesis, and perturbing the pathogen's environment via competition of space and food, and application of photodynamic therapy can help to manage the burden of oral candidiasis.

Introduction

Human microbiota is a collective colonisation of microbes on the human body that may offer beneficial or harmful effects depending on the physiological condition of the host. Understanding the roles of microbial flora in human health and disease is cardinal especially in disease prevention/management and has been the central focus of the Human Microbiota Project [1]. These microorganisms (bacteria, fungi, protists, and viruses) in the human microbiome are predicted to surpass human cells by tenfold [2], they possess divergent compositions and perform important functions through the formation of various aggregates in different anatomical body sites such as the skin, respiratory tract, gut mucosa, vaginal mucosa and oral cavity [3]. The symbiotic relationship that exist between humans and microbial flora is so important in maintaining a healthy homeostatic balance with the host. But once the existing natural microbial habitation is disrupted, in case of the presence of predisposing risk factors such as compromised host immune system and other environmental stresses that may include changes in pH, nutrient availability, temperature, and exposure to antimicrobial chemicals, microbial flora may evolve into opportunistic pathogens. Once that happens, the resultant infections may range from acute to chronic or mild to life threating infections.

The oral cavity harbours a wide range of microbiota that may cause varying degrees of oral infections in individuals with risk factors such as denture wearing, broad-spectrum antibiotic utilisation, extreme age (young and old), HIV/AIDS, cancer treatments, organ transplantation, diabetes and corticosteroid use. A number of medically important *Candida* species such as *C. albicans, C. glabrata, C. parapsilosis, C. krusei*, and *C. tropicalis* form part of the oral microbiota and their uncontrolled proliferation in debilitated immunity, causes infections. Moreover, these species are known to form biofilms which produce drug susceptibility features that differ from their planktonic counterparts [4]. Among these species, *C. albicans* has been reported as the commonest cause of oral candidiasis [5–7], and its propensity to form biofilms has led to the emergence of antifungal resistance to commonly utilised agents such as azoles, echinocandins, amphotericin B and flucytosine [8–10].

Oral candidiasis is a fungal infection mostly caused by *C. albicans* in immunocompromised individuals or those with otherwise altered immune responses and it is the commonest oral mucosa

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fungal infections [11]. The clinical presentations of oral candidiasis include erythematous candidiasis, pseudomembranous candidiasis, median rhomboid glossitis, angular cheilitis and candidal leukoplakia [5,12]. Additionally, pseudomembranous candidiasis can be classified as acute or chronic infection, and clinically appear as white or yellow plaques on mucosal surfaces [13]. Some factors such as impaired salivary gland function, dentures, malignancies, and immunosuppressive conditions tend to determine the incidence of the infection which can be managed by thorough examination and use of suitable antifungal treatment [5]. However, the chronicity of this oral infection arise owing to the debilitated host inability to clear off or minimize biofilm formation and spread. Like pathogenic bacterial biofilms, the tolerance of antifungal agents by *C. albicans* biofilms is a source of concern in clinical settings.

Biofilms are surface associated aggregates of microbes that collectively behave in a similar pattern with the ability to produce extracellular polysaccharides. These biofilms are composed of a compressed mesh of yeasts, hyphae and pseudohyphae covered in a self-produced matrix of extracellular polysaccharides [7,14]. The process of biofilm formation begins with [1] adherence of a cell to the substratum, [2] proliferation of the attached cells, forming microcolonies and deposition of an extracellular matrix, and [3] the transition of yeast cells to filamentous types (*i.e.* pseudohyphae and hyphae) and wrapped in the exopolymeric matrix [15]. Thus, adherence/colonization, filamentation and matrix production describes candida biofilm development while its pathogenicity has been related to hyphal formation [16]. This ability of biofilm formation by the fungus *C. albicans*, has contributed to its exhibited resistance to commonly utilised antifungal agents. Interestingly, planktonic cells are susceptible to most antifungal agents while their biofilm counterpart may exhibit resistance [17]. This could be due to the behavioural transition between planktonic and biofilm cells like reduced growth rate (dormant or hibernation state). Moreover, production of polymeric matrix tends to shield biofilm cells from drug penetration, and the slow growth rate promotes robust biofilm formation which play a pivotal role in the persistence of infection [18]. On the other hand, hyphae formation is an essential factor of *C. albicans* that facilitates tissue invasion leading to tissue injury [16,19]. Suppressing hyphae formation may reduce the pathogenicity of *candida* species and disrupting biofilm development may as well reduce the resistance pattern of the fungi. The existence of *C. albicans* in biofilm, the ability to produce hyphae and the ability to adhere to mucosal and indwelling medical implants makes it a causative agent for candidiasis [18]. Therefore, antimicrobial agents or strategies with the capacity to suppress dimorphic switching and modulate biofilm development can regulate and maintain the homeostatic balance of microbial flora, thereby protecting the host from candidiasis [20]. Since the resistance pattern in candida biofilm related infections are widely spread to several classes of antifungal agents [8–10], identification of potential antifungal agents or alternative strategies is much needed. Therefore, this review present some potential and alternative therapies that can be utilised to manage biofilm formation in oral candidiasis.

Anti-candida biofilm therapy

Streptococcus mutans biomolecules therapy

Fungi and bacteria can coexist to increase the frequency or severity of diseases. Numerous studies have found bacteria increasing the survival of *C. albicans*, a phenomenon that may have fortified the fungus against antimicrobial attack *via* formation of robust biofilms. A mixed culture of *C. albicans* with oral streptococci tend to form robust mixed-species biofilms *via* specific cell surface factors which are facilitated by protein-protein and lectin-carbohydrate interactions as well as hydrophobic and electrostatic interactions [21]. Moreover, the coexistence of different species does not necessarily support the mutualistic habitation but introduces also a "survival of the fittest" principle where microorganism produces certain products to increase their survivability in hostile environments as well as to establish dominance over their intra- and interspecies counterparts. This shows that the dominant organism produces biomolecules that suppress the growth or neutralising the virulent factors of the other organism. A clearly understanding of this competition behaviour and hijacking the mechanism especially by isolating the active biomolecules and use them as supplements, may allow microbes to kill themselves. This dominance behaviour exits between the oral pathogens, *Streptococcus mutans* and *C. albicans*. For instance, *Streptococcus mutans* produces a fatty acid signalling molecule trans-2-decenoic acid that was found to inhibit hyphae formation by *C. albicans* cells [22]. In another study, *Streptococcus mutans* (UA159) inhibited the formation of hyphae by *C. albicans* but supported cell growth *in vitro* biofilms [23], and this inhibitory effects was later attributed to a natural peptide, mutanobactin A from *S. mutans* UA159 strain [24]. Barbosa et al. [25] reported the inhibitory activities of *S. mutans* products on biofilm formation of *C. albicans* in *Galleria mellonella* larvae. In this study, larvae were infected with *C. albicans* and results revealed a death rate of 100% after 24 h post-infection in control group but larvae inoculated with *S. mutans* (10^5 cells/larva) or bacterial filtrate improved the survivability of *G. mellonella* larvae through blocking the hyphae formation thereby decreasing the pathogenesis of *C. albicans*. As hyphae is associated with the tissue invasion and pathogenesis of *C. albicans*, blocking it may render the fungus harmless. Therefore, identification and isolation of these naturally produced biomolecules can assist in managing candida associated infections including oral candidiasis.

Lactoferrin supplementation therapy

Lactoferrin, a glycoprotein in the family of transferrins, has a high iron binding affinity and is one of the nonspecific host defense factors present in saliva that exhibit antifungal, antibacterial, antiviral and antiparasitic activities [26]. Also, high concentration levels of lactoferrin are found in colostrum human milk [27]. The utilisation of lactoferrin alone or in combination with conventional antifungal agents has been reported with successful suppression of *C. albicans* growth in various *in vitro* and *in vivo* studies. For instance, the synergistic effect of lactoferrin with fluconazole, amphotericin B, and 5-fluorocytosine against clinical isolates of *Candida* species, revealed stronger effects with fluconazole combination exhibiting 50% inhibition rate against tested *Candida* species [28], and Kobayashi et al. attributed the purported synergism to the iron-chelating function of lactoferrin [29]. Therefore, it is conceivable that the iron-deprivation role of lactoferrin when combined with the cell membrane ergosterol interference effect of azole agents may produce enormous cell growth inhibition thereby repressing *C. albicans* overgrowth. In another study involving immunosuppressed mice, orally administration of bovine lactoferrin alleviated oral candidiasis [30], showing the effectiveness of lactoferrin against *C. albicans*. Furthermore, the incorporation of 0.3% solution of human lactoferrin in drinking water protected lactoferrin knockout (LFKO−/−) mice from oral *C. albicans* infection [27]. These studies reveal that lactoferrin is a valuable component of innate immunity that can be used to prevent *C. albicans* associated infection.

Further studies involving human subjects have also supported the protective properties of lactoferrins. For instance, a clinical study using mucoadhesive lactoferrin tablets alleviated oropharyngeal candidiasis and the method applied maintained the effective