Probiotics and Oral Candidiasis

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Oral candidiasis (OC) is an increasing health problem due to the introduction of new drugs, population aging, and increasing prevalence of chronic illness. The intake of probiotics can have a beneficial effect on OC and that the effects could vary according to the patients' characteristics.

Keywords: Candida spp. ; oral candidiasis ; Candida spp. treatment ; Candida spp. prevention ; Candida spp. carriage ; probiotics ; microbiota ; Bayesian meta-analysis

1. Introduction

Candida spp. represent a commensal yeast belonging to the normal microbiota localized on the surface of different body sites (skin, oral cavity, and the gastro-intestinal, uro-genital, and respiratory tracts) of human beings [1]. Candida spp. colonization of the mucus membranes occurs very early in life, usually at birth [2]. Under specific conditions, the fungus can switch from a harmless form into a pathogenic form that can lead to infections [3]. About 75% of healthy adults carry Candida spp. in the mouth; when there is a detection of a salivary Candida spp. count >400 colony-forming units (CFU) per mL, an infection occurs called "oral candidiasis" (OC) [4]. OC is predominantly caused by Candida albicans and by other species like Candida parapsilosis, Candida metapsilosis, Candida tropicalis, Candida khmerensis [5], Candida glabrata [6], and Candida dubliniensis [7]. Using a clinical evaluation, we can identify different Candida spp. infection phenotypes: pseudomembranous, erythematous, hyperplastic, angular cheilitis, median rhomboid glossitis [8][9], denture stomatitis [10], and linear gingival erythema [11]. All these conditions can determine a widespread spectrum of symptoms ranging from asymptomatic to very severe (such as burning sensation, pain, lesions, and bleeding), leading to discomfort in mastication, thereby limiting the food intake.

OC incidence is growing in the last few decades, because of the increase in some immune-correlated chronic illnesses (diabetes, cancer, human immunodeficiency virus (HIV)) and the intensive use of some drugs, such as antibiotics, chemotherapy, and immunosuppressants [12]. Some of major factors contributing to OC development are summarized in **Table 1**.

Table 1. Factors related to oral candidiasis (OC).

Factors Related to Oral Candidiasis
Iatrogenic factors
Antineoplastic agents [12]
Broad-spectrum antibiotics [13]
Inhaled corticosteroids [14]
Substance abuse [15][16]
Health conditions
Anemia [17]

Factors Related to Oral Candidiasis
Immunosuppression status [18]
Nutritional deficiencies [13]
Xerostomia [19]
Diseases
Cancer [20]
Cushing syndrome [13]
Diabetes mellitus [21][22]
Human immunodeficiency virus (HIV) [23]
Other factors
Age [17]
Denture wearing [20]
Pregnancy [24]
Smoke [16]

Sometimes, the superficial infection can spread out into the body, into the blood stream, causing deep and invasive candidiasis, which is associated with high hospitalization rate and even mortality [13]. The available pharmacological treatments (e.g., antifungal drugs) are very effective but present some critical points, such as frequent side effects and, in particular, antifungal resistance [1]. Therefore, it would appear critical to develop new prophylactic and complementary therapeutic strategies. The intake of probiotics seems a promising method in order to achieve these purposes. In fact, they can modulate the gut microbiota and its cross-talk with immune response, with local (intestinal) and systemic relapses [25][26][27][28][29].

Probiotics, that were identified and studied at the end of 19th century by various scientists such as Metchnikoff, Tissier, Grigorov, and Shirota, are defined as “live microorganisms that, when administered in adequate amount, confer health benefit to the host” [30]. The most used probiotics belong to Lactobacillus spp. and Bifidobacterium spp. and, to a lesser extent, to Saccharomyces spp., Bacillus spp., and Escherichia spp. [31]. The beneficial proprieties of probiotics are supported by various in vitro and in vivo studies, which used different bacterial strains (single or in combination), at different dosages [31][32]. Various studies proved the preventive and therapeutic effects of good bacteria, some of which involve metabolic functions such as fermentation of indigestible fibers [33], short-chain fatty-acid production [34], lactose tolerance [35], vitamin production [36], and reduction of cholesterol levels [37]. In addition, good bacteria have antimicrobial activity (such as competitive inhibition of pathogens [38]), produce bacteriocins [39], have antitoxin effects [40], and enhance the intestinal barrier function [41] (e.g., increased production of mucins, tight junction proteins, and goblet and Paneth cells [42]). Finally, commensal bacteria exercise immune modulation (such as the stimulation of immunoglobulin A (IgA) production, increased production of anti-inflammatory cytokines, and induction of regulatory T cells [42]).

These probiotics' proprieties suggested their use for the treatment and prevention of many medical conditions (diarrhea, constipation, inflammatory bowel disease, irritable bowel syndrome, allergic disease), sometimes with excellent results [31]. In addition, probiotics also showed an antifungal action and were successfully used in mucosal candidiasis, as reported in an in vivo study by Wagner in 1997 [43].

Sookkhee et al., in 2001, studied the effects on Candida albicans growth of different lactic-acid bacteria isolated from the oral cavity of volunteers and found that two strains, Lactobacillus paracasei and Lactobacillus rhamnosus, had the strongest effect on the yeast [44].

Lactobacillus reuteri is a promising bacterium (especially DSM 17938 and ATCC PTA 5289) for its anti-Candida properties, confirmed by several studies. In one of these, Lactobacillus reuteri was demonstrated to be able to reduce Candida load in vivo through co-aggregation, modification of oral pH with production of lactic acid and other organic acids that inhibit the virulence of Candida cells, and production of H2O2 [45].

In a recent in vitro study by Coman et al. (2014), the strains Lactobacillus rhamnosus IMC 501 and lactobacillus paracasei IMC 502, alone or in combination, showed an inhibitory effect on Candida spp. growth [46].

Lactobacillus delbrueckii ssp. bulgaricus B1 and Lactobacillus delbrueckii ssp. bulgaricus TAB2 were found to fight Candida, releasing high amounts of lactic acid [47].

Recently, it was found that Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 modulate Candida glabrata virulence, through the complete inhibition of fungal biofilms [48].

In addition, Lactobacillus acidophilus ATCC 4356 was found to inhibit the biofilm formation of fungus through in vitro experiments [49]. Biofilm formation is probably reduced through the production of substances called "bacteriocins" by probiotics. Wannun et al. reported the isolation of a bacteriocin, called "fermencin SD11", from Lactobacillus fermentum SD11, a human oral Lactobacillus, which has a strong inhibitory effect on oral Candida cells [50].

In 1997, Wagner et al. showed that the administration of probiotics could be a prophylactic and therapeutic strategy for mucosal candidiasis [43]. They demonstrated that the presence of four strains of bacteria (Lactobacillus acidophilus, Lactibacillus reuteri, Lactobacillus casei GG, and Bifidobacterium animalis) in the gastro-intestinal tract of immunodeficient mice reduced the number of Candida albicans cells, as well as the incidence and severity of mucosal and systemic candidiasis, prolonging their survival [43].

In a murine model, Matsubara et al. inoculated Candida albicans in the oral cavity and subsequently administrated an antifungal drug (nystatin) or probiotics (Lactobacillus acidophilus and Lactobacillus rhamnosus). At the end of the experiment, colonization by yeast cells was lower in the group that received probiotics (particularly L. rhamnosus) than in the group treated with nystatin [51].

In conclusion, even if the mechanism of probiotics' antifungal effect remains to be fully elucidated, some authors explored it in vitro and in vivo studies, showing that these bacteria may contrast Candida spp. infection through different and synergistic mechanisms of action.

2. Current Insights on Probiotics and Oral Candidiasis

Currently, fungal infections are widespread, especially in developed countries. A higher incidence of Candida spp. infections is associated with some predisposing factors such as the use of dentures, malnutrition, endocrine disorders, smoke, and some chronic diseases such as diabetes, HIV infection, and cancer [52]. The anti-OC treatment is mainly based on antifungal drugs, but different clinical types of OCs and the increasing number of multi-resistance phenotypes of Candida spp. represent current threats for public health. Consequently, the development of alternative therapeutic or complementary measures appears necessary to prevent the emergence of fungal resistance [53].

Many studies demonstrated that probiotics represent an efficient alternative treatment against Candida spp. infections. Moreover, they are easy to use and, thus, these products are usually well accepted by the patients [54]. The present study provides an overview of the literature on this issue, as well as a quantitative analysis that combines the results of independent studies of different design.

Both the meta-analysis on the 12 selected studies and the meta-analysis conducted on the subset of the RCTs indicated that the treatment had a beneficial effect on reducing oral Candida spp. counts.

As expected, the heterogeneity among studies was relevant because we combined studies of different design, which focused on different populations, used different treatments and doses, and were affected by different kinds and levels of bias. Our sensitivity analyses highlighted that part of the observed heterogeneity could be due to an actual difference of the treatment effect when used in different populations. For example, we found that the effect on denture wearers was larger than the effect estimated on non-denture wearers. The result on denture wearers relied only on two RCTs and should be interpreted with caution, but it is suggestive of a true difference. The larger reduction in the number of Candida spp. colonies in these patients could be caused by the direct application of probiotic products on the denture surface [55]. This hypothesis supports the idea that a lower effect of probiotics could be due to the low frequency of usage, number of probiotic cells, and delivery system, which exert an effect on the period of probiotics maintenance at the oral cavity. In this sense, the development of a mucoadhesive buccal drug delivery system [56], in order to enable the prolonged retention at the site of action, could improve the therapeutic outcome. An indication in favor of the relevance of the number of doses per day seems to arise also from the comparisons of the ORs in our meta-analysis. If we focus on RCTs on non-denture wearers, a larger effect was reported in Li et al. (2014) [57], where the treated patients received three doses per day instead of one or two. Three doses were administered also in Keller et al. 2018 [58], but this study was affected by recruitment problems, and the result relied on a very small number of subjects.

A second relevant source of heterogeneity was related to the fact that different microbial probiotic strains could have different effects on the reduction of Candida spp. counts [59]. For example, Matsubara and colleagues found that, in a mice model, the treatment with Lactobacillus rhamnosus Lr-32 was more effective than the treatment with Lactobacillus acidophilus on the Candida spp. colonization levels [51]. Unfortunately, as the number of studies collected from the literature was too small to build a network of comparisons involving multiple treatments, we considered all treatments as having the same effect, which was clearly a very strong assumption.

Therefore, summarizing the obtained results, we can conclude that probiotics have a protective role in the Candida spp. infection and especially colonization. As previously reported, the anti-Candida properties can be explained in different ways, such as (a) through co-aggregation, modification of oral pH, and production of H2O2 [45], (b) through releasing high amounts of lactic acid [47], and (c) through the complete inhibition of fungal biofilms [48][49]. However, these positive effects are highly linked to the administration method, the dosage, and the used probiotics strains. In addition, we did not find studies on prebiotics and synbiotics eligible for our meta-analysis. The effect of these products on the oral candidiasis must be better investigated in order to discover novel antifungal effects. In fact, some studies demonstrated that the combination of probiotics and prebiotics (synbiotics) can be very effective in infections [60][61].

Our results suggest planning a new clinical study to evaluate the real effectiveness of probiotics treatment in Candida spp. infection. The focal points of the study should be (1) the age stratification of the patients (old or adult), (2) the administration method (topic or oral), the type (lozenges or capsules), the dosage, and the treatment duration, (3) the choice of appropriate probiotic strains (Lactobacillus spp., Bifidobacterium spp., Saccaromyces spp., or Propionibacterium spp.), and (4) the length of the patient follow-up.

Our study also had other limitations. Firstly, the number of studies included in the meta-analysis was small, in particular when we focused on the RCTs. Secondly, some of the studies had a high risk of bias. Thirdly, with the aim of providing an overview of the literature, we did not apply strong exclusion criteria, at the price of a larger heterogeneity among studies. For the same reason, we sometimes had to adopt approximations to obtain a common comparable effect measure (OR) from the results reported in the original papers; this could have introduced a certain degree of bias in the meta-analysis.

3. Conclusions

In conclusion, our meta-analysis is one of the first that critically evaluated the impact of probiotics in oral candidiasis and, on the basis of the meta-analysis results, despite the high heterogeneity among studies, we are confident in declaring that the treatment can have a beneficial effect on reducing oral Candida spp. counts.

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