

Lactobacillus Rhamnosus, as a Potential Candidate against Candidiasis

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Abstract

Candidiasis is one of the prevalent reproductive diseases in reproductive-aged women that can be fatal. The disease is caused by *Candida spp.* *Lactobacillus spp.* are gram-positive, facultative, non-sporulating and rod-shaped bacteria Generally Recognized as Safe (GRAS) and applied as probiotics. The antifungal activity of *Lactobacilli* is a controversial subject not well understood. Therefore, it would be interesting to study the antifungal activity of vaginal and uterine strains of *Lactobacilli*, and to screen for the superior *Lactobacillus* strains with higher lactic acid production, higher antibacterial as well as antifungal potential, and to improve them via the generation of the transformants that express and secrete the antifungal as well as antibacterial peptides such as metchnikowin.

Keywords: Bio-control; *Candida*; Metchnikowin; Probiotic; Peptide

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Opinion

Candida species are a major cause of morbidity and mortality worldwide and represent a serious threat to public health [1-3]. These opportunistic pathogens can cause vaginitis, oral candidiasis, cutaneous candidiasis, candidemia, and systemic infections [4]. Candidemia is the most frequent hospital infection accounting for up to 15% of bloodstream infections and *Candida spp.* are the main causal agents in 50-70% of systemic fungal infections [5-7]. Despite the danger of the disease, the available drugs have not been enough efficient. For example, 90-day survival following the diagnosis of candidemia varies between 55% and 70%, depending on the underlying condition of the patient and the specific species causing infection [8]. The occurrence of human immunodeficiency disease, the use of immunosuppressive medications applied in neoplastic surgeries, diabetics, dialysis, severe burns, abdominal surgery, and the use of corticosteroids, cancer chemotherapeutics, and antibacterial antibiotics [9]. Most recently the bacterial flora of uterus in healthy females and ill females has been reviewed [10], where significant differences in the diversity of the bacteria have been noticed [10].

Based on this valuable review, *Bacillus*, *Blautia*, *Desulfosporosinus*, and *Parabacterioides* are only found in healthy uterus. *Burkholderia*, Chitinopagaceous bacteria, *Pelomonas* and *Rhodanobacter* are associated with female infertility. *Moraxellaceous* bacteria, *Streptococcaceous bacteria*, Sphingobium and Vagococcus are especially found in the uterus of the females suffering from endometriosis. Anaerococcus and Parvimonas are only found in the uteri with chronic endometriosis, while Euryarchaeota only in the uteri with polyps. The bacteria from the genera *Anarostipes*, *Anaerotruncus*, *Arthrospira*, *Cloacibacterium*, *Peptoiphilus*, *Porphyromonas*, *Ruminococcus* and *Treponema* are only isolated from uteri with cancer [10].

Although bacteria only found in healthy uteri seem to be the most proper choices for the biological control of uterus candidiasis, however, only bacteria from the genus *Lactobacillus* are found in all uteri but those with cancer. It seems that these bacteria can survive under various physiological conditions inside uteri, and therefore, these bacteria can be selected for engineering the bacterial flora of uterus. Recently a strain of *Lactobacillus rhamnosus* PBL005

has been known to be of probiotic potentials in gynecological health. The bacterium reduces the level of pathogenic bacteria such as *Propionibacterium acnes* and *Streptococcus agalactiae* [11]. Additionally, women vaginally colonized with *Lactobacillus*-dominated microflora are less likely to acquire HIV from their male partners [12] and indicate reduced viral shedding into the lower FRT [13] that could protect against the sexual transmission of HIV to their male partners and to vaginally delivered neonates [14]. The lactic acid produced at physiological concentrations exhibits a broad-spectrum HIV viricidal activity [15]. Although both enantiomers of the acid exhibit similar viricidal activity against HIV-1 at 1% (w/w), however, L-lactic acid is 17-fold more potent than the D-isomer at the threshold concentration of 0.3% [15]. Similarly, women with dominant vaginal *Lactobacilli* are less likely to be infected with herpes simplex virus-2, HSV-2 [13].

While most of these gram-positive bacteria of the genus are generally recognized as safe (GRAS) [16], they have been reported as effective antagonists of pathogenic fungi [17]. The role of *lactobacillus* species as a barrier to prevent vulvovaginal candidiasis diseases caused by *Candida* species is controversial [18]. Based on *in vitro* studies, *Lactobacilli* are believed to play this preventive role either by the production of antimicrobial factors or via the competition with *Candida* species for adhesion sites on the mucosa [19]. Regarding the mechanism of the antagonism, there is evidence that the growth of *Candida albicans* is inhibited by lactic acid produced by *lactobacilli* at low pH [20] or is not inhibited [21]. Vaginal *Candida* species demonstrate different levels of acid tolerance and adapt to low acidity through several mechanisms, including high plasma membrane proton pump activity [22]. Thus, the ability of lactic acid to inhibit *Candida* growth may depend on the level of acid tolerance of an individual species.

Despite these *in vitro* data, epidemiological studies do not support a protective role for vaginal *Lactobacillus* species against vulvovaginal candidiasis. Colonization of the vagina with *Candida* species is more common in the women with BV [23]. Furthermore, a prospective study has indicated that vaginal *Lactobacilli* do not protect against vulvovaginal candidiasis while BV affords protection [24]. Natural antimicrobial peptides are considered as inspiration for design of a new generation antifungal compounds [25], a goal that necessitates the innovation of new methodologies for the practically effective application of antifungal peptides. It is possible to increase the antagonistic potential of *L. rhamnosus* PBL005 via generation of the transformants that express antifungal peptide transgenes and secrete the antifungal peptides against *Candida spp.* Such an activity could be an important step toward the application of the bacterial strain in the practical restructuring the microbial flora of the vagina and uterus. Therefore, it would be interesting to isolate *Lactobacillus rhamnosus* strains, screen them for their antibacterial activity against pathogenic endometrial bacteria and to test their antifungal activity against pathogenic *Candida spp.* The antimicrobial peptides can be applied in the enhancement of their biological control potential against microbial pathogens. One of these peptides is metchnikowin, a 26 amino acid proline-rich

peptide produced by *Drosophila* that exhibits antimicrobial activity against fungi as well as gram negative bacteria [26].

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