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Profiles and technological requirements of urogenital probiotics

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ABSTRACT

Probiotics, defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host, are considered a valid and novel alternative for the prevention and treatment of female urogenital tract infections. Lactobacilli, the predominant microorganisms of the healthy human vaginal microbiome, can be included as active pharmaceutical ingredients in probiotics products. Several requirements must be considered or criteria fulfilled during the development of a probiotic product or formula for the female urogenital tract. This review deals with the main selection criteria for urogenital probiotic microorganisms: host specificity, potential beneficial properties, functional specifications, technological characteristics and clinical trials used to test their effect on certain physiological and pathological conditions. Further studies are required to complement the current knowledge and support the clinical applications of probiotics in the urogenital tract. This therapy will allow the restoration of the ecological equilibrium of the urogenital tract microbiome as well as the recovery of the sexual and reproductive health of women.

Contents

Abbreviations: API, Active pharmaceutical ingredients; AV, Aerobic vaginitis; BV, Bacterial vaginosis; CFU, Colony forming units; CRL, Centro de Referencia para Lactobacilos Culture Collection; CVF, Cervicovaginal fluid; EFSA, European Food Safety Authority; FGM, Food Grade Microorganisms; FGT, Female genital tract; GRAS, Generally tegarded as safe; HM, Human microbiome; ISAPP, International Scientific Association for Probiotics and Prebiotics; LAB, Lactic acid bacteria; PAMP, Molecular patterns associated with pathogens; QPS, Qualified presumption of safety; TLR, Toll-like receptors; UGTI, Urogenital tract infections; UTI, Urinary tract infections; VVC, Vulvovaginal candidiasis.

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1. Introduction

Human beings are colonized by a diverse and complex collection of microbes, contributing all of them to host nutrition, development of the immune system, response to pathogens and mucosal cell differentiation and proliferation. The knowledge of these communities and their gene contents has been referred collectively as the *human microbiome (HM)*, supported by a NIH-funded project consortium [1,2]. The human microbiome is a complex system of many microbial communities inhabiting a diversity of environmental niches throughout the human body. Until recently, technological limitations precluded the global characterization of the human microbiome in terms of composition, diversity and dynamics. Massive parallel sequencing and other high throughput approaches have offered novel ways to explore and examine the microbiota from different human body cavities that includes eukaryotes, archae, bacteria and viruses. The sequences of more than 1000 bacterial genomes are now available and it is interesting to remark that bacteria numbers within an individual are estimated higher than number of human cells by an order of magnitude [1–3].

The increase in microbiota-related research has provided important advances toward the identity of specific microorganisms and microbial groups or microbial molecules, their functions and relationships between healthy-unhealthy status, being essential to the overall health of the host by performing relevant physiological functions, protection against pathogens and driven the development of the immune system during neonatal life. Additional projects are investigating the association of specific components and dynamics of the microbiome with a variety of disease conditions. HM project encountered an estimated 81-99% of the genera, enzyme families and community configurations occupied by the healthy western microbiome [1,2]. Studies on this HM have revealed that healthy individuals differ remarkably in the microbes that occupy gut, skin and vagina. But the microbial genera are highly dependent on the colonization of microorganisms carried out after the newborn delivery, on the prevalent environmental conditions and on different host factors that are modified through the time. There is some remarkable similarities in the bacterial species present in people with different ethnicity [3,4].

The microbiome colonizing the human body provides the host a huge coding and metabolic activities as will be described later [1,2,5–8]. Among this microbiota there are health-promoting indigenous species that are commonly consumed as live supplements [9].

Lactic acid bacteria (LAB) and some related genera were isolated from almost all the mucosa and human tracts. Referred specifically to the genus *Lactobacillus*, there are around 202 different described species up to present (http://www.bacterio.net/lactobacillus.htlm) and more than 100 with their chromosomal DNA sequenced. Their genomes have sizes varying from 1.8 to 3.3 MB, and their G+C content range from 33 to 51%. In such a way, a *Lactobacillus* core genome has been described, constituted by 383 sets of orthologous genes, designed as *Lactobacillus* core genome [5,10,11].

2. Vaginal microbiome. Ecological and functional aspects

Vaginal microbiota forms a mutually beneficial relationship with their host and has a major impact on health and disease. In the vaginal microbiome, lactobacilli constitute the dominant proportion (80%) of bacteria inhabiting the healthy women's vagina [1,2,5–7,12,13]. Some LAB strains have found to be endogenous from healthy human vagina, where there is a rather stable microbiota [14–16]. LAB members are consistently detected in healthy vaginal microbiota of different ethnic groups and/or women living in different geographical locations [7,17–22]. Four main species were identified: *Lactobacillus crispatus, Lactobacillus iners, Lactobacillus jensenii* and *Lactobacillus gasseri*, along with other lactobacilli at lesser extent, as *Lactobacillus acidophilus, Lactobacillus ruminis, Lactobacillus rhamnosus* and *Lactobacillus vaginalis* [7,15]. Our understanding of the vaginal microbial community composition and structure has significantly broadened as a result of studies using cultivation-independent methods based on the analysis of 16S ribosomal RNA (rRNA) gene sequences [6,10,11,15,23,24].

The high abundance of LAB is strongly associated with a healthy vagina, whereas a low abundance of LAB is more prevalent in women with a pathological condition [6–9,13,14,16,19,25–27]. Eventhough the four species indicated above are predominantly detected in human vagina, co-dominance between LAB is not very frequent [1,7,15]. In asymptomatic, otherwise healthy women, several kinds of vaginal microbiota exist, the majority often dominated by species of *Lactobacillus*, while others are composed of a diverse array of anaerobic microorganisms [7,8,13,15,21,27]. Ravel et al. [7] characterized the vaginal microbiome of asymptomatic, sexually active women who represented four ethnic groups (white, black, Hispanic, and Asian). The vaginal bacterial communities were classified according to community composition in five major groups. Communities in group I were dominated by *L. crispatus*, whereas groups II, III and V were dominated by *L. gasseri*, *L. iners* and *L. jensenii*, respectively. Group IV was highly heterogeneous and had higher proportions of strictly anaerobic bacteria, including *Prevotella*, *Dialister*, *Atopobium*, *Gardnerella*, *Megasphaera*, *Peptoniphilus*, *Sneathia*, *Eggerthella*, *Aerococcus*, *Finegoldia*, and *Mobiluncus*. The proportions of each community group varied among the four ethnic groups. Communities with high Nugent scores (criterion used to diagnose bacterial vaginosis) were most often associated with communities in group IV, but were also observed in communities belonging to other groups.

Most of the *Lactobacillus* species described above were related to the healthy vagina, but some other authors suggested that *L. iners* was frequently isolated from non-healthy subjects [24]. Molecular-based and culture-based techniques used in combination have indicated that in the absence of lactobacilli, normality can be maintained by more fastidious lactic acid producing bacteria [15]. The dominant *Lactobacillus* species may differ racially or geographically, but the principle of numerical dominance persists [6,7,17,18,20–22,27], indicating that the LAB may be adapted to the vagina and possess characteristics enabling them to thrive in that environment [28].

The temporal dynamics of vaginal communities are poorly known because few studies have been done in which the same individuals are frequently sampled and variation in community composition assessed over time using cultivation-independent methods [24,26,29,30]. Fredricks [31] suggested that the vaginal microbiota can be highly dynamic, with dramatic shifts in bacterial composition and concentrations in response to numerous endogenous and exogenous factors. Ravel et al. [7] proposed different hypothesis that could explain the

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