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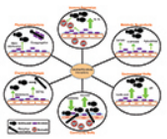

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REVIEW

# The vaginal mycobiome: A contemporary perspective on fungi in women's health and diseases

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**ABSTRACT**

Most of what is known about fungi in the human vagina has come from culture-based studies and phenotypic characterization of single organisms. Though valuable, these approaches have masked the complexity of fungal communities within the vagina. The vaginal mycobiome has become an emerging field of study as genomics tools are increasingly employed and we begin to appreciate the role these fungal communities play in human health and disease. Though vastly outnumbered by its bacterial counterparts, fungi are important constituents of the vaginal ecosystem in many healthy women. *Candida albicans*, an opportunistic fungal pathogen, colonizes 20% of women without causing any overt symptoms, yet it is one of the leading causes of infectious vaginitis. Understanding its mechanisms of commensalism and pathogenesis are both essential to developing more effective therapies. Describing the interactions between *Candida*, bacteria (such as *Lactobacillus* spp.) and other fungi in the vagina is fundamental to our characterization of the vaginal mycobiome.

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*Candida albicans*; fungal community; fungi; infectious diseases; microbial ecology; microbiome; microbiota; mycobiota; vagina; vulvovaginal candidiasis

## Introduction

The community of fungal organisms residing within the lower female reproductive tract is referred to as the vaginal mycobiota. Among those is one of the leading causes of vaginal infection, *Candida albicans*, a well-studied fungal pathogen. Because vulvovaginal candidiasis (VVC) is the second most commonly reported form of infectious vaginitis, a great deal of effort has been invested in studying the mechanisms of *C. albicans* pathogenesis. However, the totality of fungal organisms present within the vagina has been grossly underappreciated. While we have extensive knowledge of the types of bacteria present in the vaginal milieu, very little is known about their fungal counterparts. Recent studies that explored the composition of fungi within the vagina have pointed to an exciting new frontier of research. Exploring the types, functional and compositional dynamics of fungal species in the context of the vaginal environment is an important objective, with potential implications for treating and preventing VVC, improving obstetric outcomes, and reproductive health in general. Recent advances in next-generation sequencing tools have enabled the high-throughput identification of fungi and provide burgeoning insights into fungal ecology.

### *Mycology of the vagina*

The sum of the genomes and genes carried by fungal species that exist within a particular environmental or biological niche is termed the "mycobiome."[1] In humans, the mycobiome is poorly understood compared to the microbiome, which was extensively described by the Human Microbiome Project—the largest and most comprehensive survey of bacterial taxa in healthy adults.[2-5] In the midst of an explosive new era of genomics, rapidly developing sequencing technologies and cutting-edge bioinformatics tools, the mycobiome has developed into its own "sub-specialty" within the field of microbial genomics, but one that lags far behind its bacterial counterpart.[6]

The earliest studies of vaginal microbiology underestimated the complexity of this ecosystem, in part, due to the limitations of the culture-dependent techniques used.[7,8] While bacteria have long been known to dominate the vaginal milieu, leading to a number of studies on the bacterial community, early investigators of vaginal mycology have attempted to draw attention to the importance of fungal members of this community.[9]

Using classical, culture-dependent methods, investigators have measured point prevalence of vaginal fungi in healthy volunteers and diabetics, as well as adolescents

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and pregnant women.[10-12] Fungi were recovered by culture in 20–60% of the samples. Without exception, the predominant member of the fungal community is identified as *C. albicans* (often >70%), though the rank prevalence for non-*albicans* species (including *C. krusei, C. parapsilosis, C. tropicalis, C. glabrata, C. guilliermondii, C. pseudotropicalis, C. stellatoidea*, and others) varies by population studied, geography, and cultivation methods. More recent epidemiological studies of *Candida* carriage report even greater representation by *C. albicans*, making up 85–95% of isolates recovered.[13-15]

A study comparing *Candida* isolates from the United States and the United Kingdom concluded that physiological biotyping could not significantly distinguish the isolates examined.[16] According to the authors, the evidence does not support strain tropism—a selection for "vaginotropic" vs. "vaginopathic" strains—since strains isolated during infection are statistically identical to those collected in asymptomatic colonization.[16,17] Using these same biotyping methods Odds *et al*[17,18] reported consistency in isolates from different sites (and tissue types) in the same patient and isolates collected months apart. Using different methods, a separate group also reported that no significant differences exist among *Candida* strains isolated from different body sites; but added that a single host can be colonized by multiple species, and even multiple genotypes of the same species.[19]

Using a cultivation-independent 18S rRNA gene clone library, Guo *et al*[20] identified 3 fungal phyla in vaginal samples: *Ascomycota* (22/28), of which *Candida* was the predominant genera, *Basidiomycota* (5/28), and *Oomycota* (1/28). They reported larger proportions of *C. albicans* and lower proportions of *S. cerevisiae* and uncultured (unidentified) fungi in women with allergic rhinitis and recurrent vaginal candidiasis, as compared to healthy controls. Fungal diversity was also increased in these patient populations compared to controls. The authors suggested that fungal dysbiosis might be correlated with the pathophysiology of recurrent vaginal candidiasis, highlighting a role for fungal community in disease.

Though next-generation sequencing technology has profoundly expanded our appreciation of the bacterial microbiota within the human vagina[21], these sophisticated methods have been applied to the study of the vaginal mycobiota to a far lesser degree. In fact, the very first next-generation sequencing-based survey of fungal communities within the vagina was published in 2013 by a group whose aim was to describe the bacterial and fungal communities of women in Estonia.[22] This cross-sectional study sequenced the Internal Transcribed Spacer 1 (ITS1) in 251 vaginal samples from 294 healthy women to characterize fungal taxonomic composition. Fifty-eight percent of sequences belonged to the *Ascomycota* Division, though *Basidiomycota* was also represented in a small number of sequences (3%). Within *Ascomycota*, hits to *Saccharomycetales* (dominated by the genus *Candida*), *Capnodiales, Eurotiales, Pleosporales*, and *Helotiales* were observed. The resulting mean taxonomic richness for each sample was about 8 fungal Operational Taxonomic Units (OTUs). *Candida* OTUs could be detected in 70% of samples. Within the group of sequences mapping to *Candida, C. albicans* was not surprisingly predominant (68%). Strikingly, 161 unique hits at the species-level were obtained from this data set, yet 38% of OTUs were unspecified—no taxonomic assignment lower than kingdom was available. These results speak to a very serious problem in molecular-based fungal taxonomy. The quality and relatively low representation of fungal species in reference databases has direct consequences on quality and accuracy of taxonomic assignments returned. Current databases not only lack the rich volume of sequences that exist for bacterial 16S rRNA gene, but taxonomic synonyms and misclassifications are widespread.[23-25] To protect the integrity of these investigations, careful sequence annotation and database curation is absolutely essential. The results published by Drell *et al*,[22] nonetheless, reveal the underappreciated diversity of fungal members within the vaginal ecosystem and warrant follow-up on these findings. In light of our limited understanding of vaginal mycology, most of what we know derives from studies focused on the key player *C. albicans*.

## Fungal commensalism in the vagina

Witkin and Ledger[26] described the characteristics and qualities of the human vaginal environment that make it both unique and complex. In contrast to oft-used animal models, the vagina of reproductive-age women is distinctly acidic (pH of 4.5 or less), owing to the presence of lactic-acid producing bacteria that thrive in this anaerobic niche[27] not otherwise described in the Class Mammalia.[28] Further intricacies of the vaginal environment in humans include cycles of growth, production of glycogen and its breakdown products by human $\alpha$-amylases[29], and shedding of the epithelium in response to reproductive hormones, and primarily innate (as opposed to adaptive) mucosal immune protection.[30-32] These physiologic features are certainly key determinants of microbial colonization of the vaginal mucosa.[7,33]

In 1976, Goplerud *et al* isolated *Lactobacillus* spp and *C. albicans* at consistently increased rates over all 3 trimesters in healthy pregnant women.[34] These early observations provided preliminary evidence for a positive correlation between estrogen levels and vaginal colonization of

microbes. The data were further substantiated by Larsen and Galask[35] who demonstrated obligate estrogenization to achieve yeast colonization in a rat model of vaginal *Candidiasis*. At present, all laboratory animal models of vaginal candidiasis require estrogen-treatment to establish colonization and subsequent infection.[36, 37] Some *Candida* species possess a cytosolic estrogen receptor that could mediate direct transcriptional responses to host hormones.[38] Furthermore, estrogen has been shown to disrupt neutrophil chemotaxis to the vaginal epithelium[39] and inhibit Th17 cell differentiation,[40] resulting in heightened host vulnerability to pathogens, such as *Candida*. Clinical and anecdotal reports frequently link symptomatic *Candida* vaginitis to the luteal phase, just prior to menses, which is marked by both a high estrogen state and increased vaginal pH.[7] Researchers have documented enhanced *C. albicans* adherence to vaginal epithelial cells through estrogen signaling.[41] Further, while *Candida* is known for its broad pH-range tolerability, adherence to vaginal epithelial cells is significantly enhanced at pH 6 compared to pH 3–4.[7]

The hormone-dependent production and accumulation of glycogen (and its breakdown products[29]) by human vaginal epithelial cells should not be understated in its contribution to fungal colonization,[42] however, *Candida* can utilize other nutrients (including lactate), making *Candida* highly adaptable to shifts in the nutritional microenvironment in the vagina.[7] The food source used by *Candida* in a particular niche is not a trivial detail, as studies have clearly indicated the effects of environmental cues, such as nutrient availability, on cell wall architecture[43-45] which impacts interactions between *Candida* and immune cells. Recent *in vitro* work has shown that in the presence of lactic acid (as the sole carbon source) *C. albicans* is taken up by macrophages less efficiently and can alter immune cell cytokine profiles, specifically by increasing IL-10 and decreasing IL-17 production.[46, 47] Interestingly, cells grown in a mixed lactate-glucose media behave more like lactate-grown cells. This has particular relevance in the vaginal context because of the abundance of both glycogen (and its breakdown sugar products) and lactic acid, which could effectively promote anti-inflammatory responses to *Candida*. Other studies have corroborated these findings and suggest that *Candida* may have evolved to curb immune responses to promote its own persistence and commensalism.[48] It has also been shown that *Lactobacillus* indoleamine 2,3-dioxygenase 1 (IDO1) in the gut leads to the production of tryptophan catabolites that act on regulatory T cells, resulting in increased local expression of IL-22[49] and immunoprotection to VVC.[50] This suggests that the bacterial microbiome could be mediating tolerance to *C. albicans* on the mucosa.

Attachment to the mucosal epithelium is mediated by binding to specific host receptors, of which the ALS (agglutinin-like sequence) adhesion family is best studied.[51-53] Hyphal formation is an important attachment factor as well.[54,55] In response to quorum sensing mechanisms, yeast growth is favored by high cell densities ($>10^7$ cells $mL^{-1}$) whereas hyphal formation is stimulated by lower cell densities ($<10^7$ cells $mL^{-1}$).[53] *C. albicans* adheres to vaginal and oral epithelial cells with greater levels than other species[56]—an important, but most likely partial, explanation for the predominance of *C. albicans*-associated infections. Interestingly, Sobel *et al*[57] reported marked person-to-person variability in *Candida* adherence to exfoliated vaginal epithelial cells, but enhanced attachment of *C. albicans* to epithelial cells from women with recurrent VVC.[58]

## *Pathogenesis of* Candida *and vulvovaginal candidiasis*

Despite its prominence as the second most common vaginal infection among US women of reproductive-age,[13,59] epidemiologic data on the incidence of VVC remains incomplete—primarily because this is not a reportable infection by public health authority standards.[60] And while exceptionally common—3 in 4 women will be affected at least once over their lifetime[61]—asymptomatic carriage rates for *C. albicans* in healthy women are estimated at around 20%.[12,62] Mechanisms of immunoprotection are still debated, and the factors that trigger the transition from commensal to pathogenic yeast are still obscure. However, it is generally accepted that predispositions for *Candida* growth/invasion are niche specific[63,64], though immune defects, breaches in epithelial integrity and microbial dysbiosis are common themes.[55] While many similarities exist between the mucosal environments of the mouth and vagina, the immunology of *Candida* vaginitis is undoubtedly distinct.[65,66] Excellent reviews have been written on the immunology of VVC, thus will not be discussed here.[67-69]

A statistically significant increase was noted in number of *C. albicans* colonies cultured from swabs of women with VVC, representing an increase in fungal concentration, as compared to controls (healthy, no VVC), though no difference was measured with non-*albicans Candida* species.[70] Peeters *et al*[70] noted a positive correlation between the number of *C. albicans* colonies grown and amount/severity of vaginal discharge, as well as reported pruritus (itching). These findings support the theory of a fungal burden threshold above which inflammatory cells are recruited, resulting in the vaginal symptoms often reported, including itching, irritation, burning, and discharge.[68]

*Candida* are polymorphic fungi, whose morphogenic transitions are essential mechanisms of pathogenesis in the human host.[71,72] The yeast form (blastoconidia) is typically associated with asymptomatic colonization, transmission or spread (particularly in the bloodstream)[60,73], while the hyphal (mycelial) form contributes mostly to adherence and mucosal invasion, characteristic of symptomatic disease.[57,60,74,75] Peters *et al*[76] recently noted that the genes which control *C. albicans* morphogenesis are required for the immunopathology associated with VVC. A variety of environmental stimuli affect a cell's morphology, including nutrient availability, pH, and temperature.[72] Using sophisticated quorum sensing mechanisms, *C. albicans* regulates morphogenesis in response to these external cues.[77]

*In vitro* proteolytic activity of *C. albicans* isolates from women with symptomatic VVC was greater than isolates from asymptomatic carriers.[78] Proteolytic enzymes, namely the secreted aspartyl protease (SAP) family, are well-studied virulence factors employed by *C. albicans*, in particular, to invade the mucosal layer during VVC and induce immunopathology.[79-83] In 1940, it was proposed that the immunopathology of VVC is caused by a *Candida* toxin.[84] Decades later, researchers negated this hypothesis by suggesting *Candida* cell wall glycoproteins resemble bacterial endotoxins in their structural location, pyrogenicity and immunogenicity, though much less potent.[85] Earlier this year, however, Moyes *et al*[86] identified a secreted cytolytic peptide toxin produced by *C. albicans* that is essential for mucosal pathogenesis in a murine model of oropharyngeal candidiasis. The *C. albicans* extent of cell elongation 1 (ECE1) gene, which encodes the toxin they named Candidalysin,[86] is also among the most highly expressed genes during murine VVC.[87]

Like many pathogenic bacteria, *Candida* species in general and *C. albicans* in particular, are efficient at biofilm formation within the human host.[88,89] *C. albicans* biofilms have been identified on dentures, catheters, as well as mucosal epithelia.[90] Contact sensing (contact with abiotic or host substrates) has been described as an important trigger for *C. albicans* biofilm formation.[91] Furthermore, yeast cells are stimulated to form hyphae upon contact with a surface,[91] which in some cases may facilitate active penetration of host tissues[92,93] and in others may lead to mature biofilm formation.[94] Transcriptional regulation of biofilm formation has been mainly attributed to Bcr1, Tec1, and Efg1,[90] however, recent studies revealed novel transcription factors associated with this process: Ndt80, Rob1, Brg1.[95] Harriott et al[96] were the first to show using *in vivo* and *ex vivo* models of murine *Candida* vaginitis that *C. albicans* does, indeed, form Bcr1- and Efg1-dependent biofilms. Similar to other body sites, biofilms in the vagina are of major concern, as they have been implicated in immunopathology of VVC, anti-fungal treatment failures and recurrent infections.[97,98] Genomic microvariations in *C. albicans*, which include rearrangements, loss of heterozygosity, polymorphisms, and copy number variations, have also been associated with fungal persistence in a host and antifungal resistance.[99,100]

## Candida-*Bacteria interactions in the vagina*

As early as 1930, Doderlein's bacillus,[101] which is now widely known as *Lactobacillus*, was positively attributed to protection of the vaginal mucosa and a "healthy" microenvironment.[102] Because the lack of *Lactobacillus* spp. within the vaginal microbiota has been associated with susceptibility to urogenital infections, such as bacterial vaginosis,[103,104] HIV,[105] and urinary tract infection,[106] it stands to reason that *Lactobacillus* spp may, similarly, protect women from vulvovaginal candidiasis (VVC). Among others, Odds proposed in 1979 a model where symbiosis between some fungi and bacteria is established,[107,108] though these relationships have not been clearly elucidated within the vagina. Early bacterial-yeast co-culture experiments led to the hypothesis that the role of vaginal bacteria is not likely to prevent colonization of *Candida* but rather prevent their uninhibited proliferation.[35] In support of this hypothesis, short chain fatty acids and lactate produced by *Lactobacillus* spp. and other lactic-acid producing bacteria were shown to inhibit the yeast-to-hyphae switch in *C. albicans*.[109] Further, investigators have reported lower numbers of *Lactobacillus* spp in vaginal cultures from women with symptomatic VVC.[70,102] Supporting evidence for this hypothesis includes increased susceptibility to *Candida* vaginitis following antibiotic therapy, a well-documented risk factor for VVC.[110-112] But not all studies have substantiated the link between VVC and antibiotic usage,[113] and even anecdotal reports are inconsistent. This is consistent with the different types of vaginal microbiota which could be differentially affected by antibiotics.[114,115] Not all women who take antibiotics develop VVC and most women who report VVC have not recently taken antibacterial therapy. Colonization with *Candida* appears to be a prerequisite risk factor for developing VVC following antibiotic therapy.[116] Recently, however, one group has posited that their findings are more consistent with *Lactobacillus* being associated with greater risk for vulvovaginal candidiasis.[117] By elucidating the mechanism by which lactic acid suppresses immune responses to *C. albicans*, Ene *et al*[46] have supplied evidence for this claim.

*Candida*-bacteria interactions within the vagina likely take place within the context of a polymicrobial biofilm

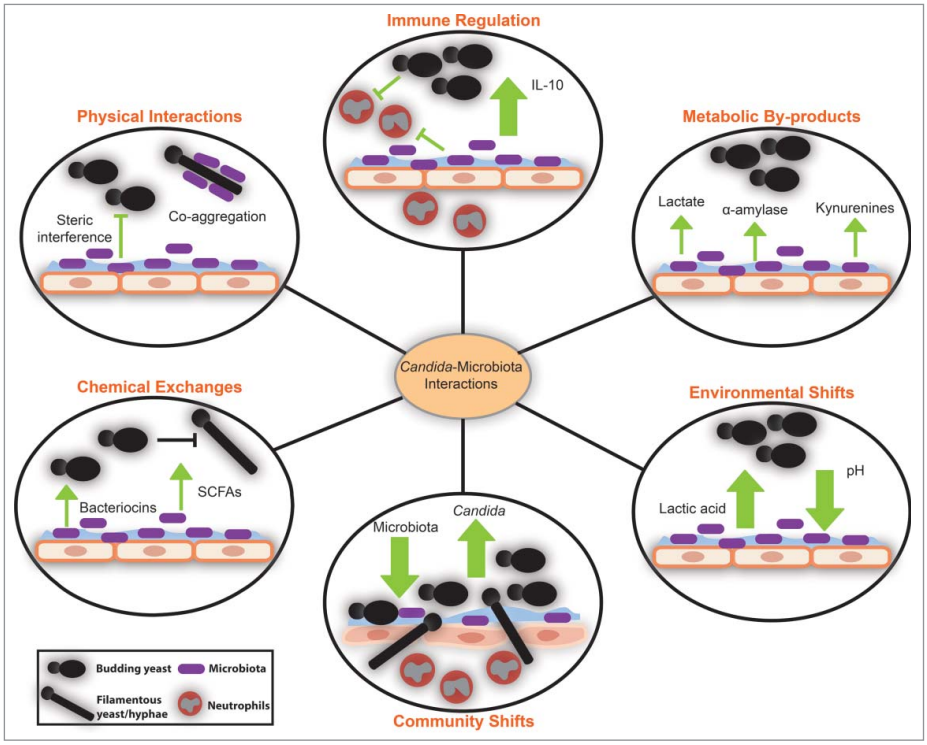


**Figure 1.** Interactions between *Candida* and microbiota at the mucosal interface have profound effects on the vaginal ecosystem.[109,120-125] Metabolites and small molecules made by the microbiota affect the metabolism and morphology of *Candida* species. Changes in microbiota relative abundance also impact the abundance of *Candida* and its ability to access the mucosal surface, where invasion occurs. In healthy states, when microbiota-derived lactic acid is produced, *Candida* can alter host cytokine production and promote anti-inflammatory signaling. The contribution of bacterial-fungal interactions to the ecology of the vaginal microbiota remains to be described.

on the epithelial surface.[118,119] An *in vitro* model of various *C. albicans*-bacterial biofilms concluded that bacteria negatively impact *C. albicans* biofilm formation by inhibiting fungal growth and suppressing genes responsible for hyphae formation.[120] Peleg *et al*[121] described 5 types of bacterial-fungal interactions and many speculate these also take place within the vagina: physical interactions,[122,123] chemical exchanges,[124] use of metabolic by-products,[109,118] changes in the environment,[124] and alteration of the host immune response.[125] Further studies are required to better understand this important relationship between vaginal bacteria, *Candida* spp. and other fungi in health and diseases.

## *Importance of the fungal mycobiome*

It is becoming increasingly clear that fungal communities play a more significant role in human health and disease than once assumed.[126,127] Concerted effort, such as that given to surveying bacterial composition and abundance, is required to carry this field into the translational and clinical arenas. Characterization of the human mycobiome has the potential to produce widespread clinical advances in diagnosis, treatment and prevention of fungal infections[23,128] and vulvovaginal candidiasis, in particular, but also potentially bacterial and viral infections. Made possible by next-generation, culture-independent sequencing technologies, new developments in fungal contribution to human health and disease have proven to be very promising. Though far less abundant than bacterial members of the environment, fungi (but primarily *Candida albicans*) have a pronounced effect on vaginal health, and thus require more in depth studies of the interaction between the mycobiome and the microbiome. While pathogenic mechanisms attributed to single fungal species have consumed much of mycology, it is believed that mycobiome studies will establish correlation between composition and function of the entire fungal community, and cross-kingdom interactions to disease processes. Notably, fungi-fungi interactions have been implicated in the pathogenic process; *C. glabrata* binds to the hyphae of *C. albicans* to establish oropharyngeal candidiasis,[129] thus supporting the need for mycobiome studies that consider the full context in which infection takes place. Culture-based isolation and characterization of pathogens remains of great necessity, however, development of novel *in vitro* (and even *in vivo*) models of polymicrobial communities would be ideal to test hypotheses into the role of the vaginal mycobiome in health and disease. And while we invest scientific capital to understand

pathogenic mechanisms, we must not neglect to appreciate mechanisms of commensalism, as this will likely lead to preventative strategies that prohibit the commensal-to-pathogen transition.[130]

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