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Review

Cross interaction between bacterial and fungal microbiota and their relevance to human health and disease: mechanistic pathways and prospective therapy

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Diverse bacterial and fungal microbiota communities inhabit the human body, and their presence is essential for maintaining host homeostasis. The oral cavity, lung, gut, and vagina are just a few of the bodily cavities where these microorganisms communicate with one another, either directly or indirectly. The effects of this interaction can be either useful or detrimental to the host. When the healthy microbial diversity is disturbed, for instance, as a result of prolonged treatment with broad spectrum antibiotics, this allows the growth of specific microbes at the expense of others and alters their pathogenicity, causing a switch of commensal germs into pathogenic germs, which could promote tissue invasion and damage, as occurs in immunocompromised patients. Consequently, antimicrobials that specifically target pathogens may help in minimizing secondary issues that result from the disruption of useful bacterial/fungal interactions (BFIs). The interface between *Candida albicans* and *Aspergillus fumigatus* with bacteria at various body sites is emphasized in the majority of the medically important BFIs that have been reported thus far. This interface either supports or inhibits growth, or it enhances or blocks the generation of virulence factors. The aim of this review is to draw attention to the link between the bacterial and fungal microbiota and how they contribute to both normal homeostasis and disease development. Additionally, recent research that has studied microbiota as novel antimicrobials is summarized.

Key words: bacteria, microbiota, fungi, diversity, host interaction, human, infectivity, disease

INTRODUCTION

For a very long time, it was believed that the presence of pathogens was primarily linked to disease. Only with the rapid progress in sequencing techniques and progress of the human microbiome project, which allow in-depth comprehension of the microbiome communities in numerous body niches, have authors begun to recognize how microbiota interact with the host and with one another in a complex, dynamic ecology, as well as the significance of the microbiota for the normal physiological functions of the human body [1].

Most human fungal infections cause superficial infections of the skin, hair, and nails, systemic infections, and persistent fungal lung infections. These infections are commonly seen in cases of immune system suppression. Certain members of the human microbiota, such *Candida albicans*, which colonizes the mouth, urogenital tract, and gastrointestinal tract, are among these opportunistic invaders. Other environmental reservoirs include *Cryptococcus neoformans* and *Aspergillus* species (spp.) [2].

Within the microbiome, interactions between fungi and bacteria can be either antagonistic or synergistic. Many illnesses, such as diabetes, allergies, autism, obesity, cystic fibrosis (CF), inflammatory bowel disease (IBD), and colorectal cancer (CRC), are associated with an imbalance in the human microbiota. Age, food habits, stress, long-term inflammation, overuse of broad-spectrum antibiotics, underlying diseases, and change in the composition, function, and metabolic activity of the microbiota are all linked to this dysbiosis [3].

Amongst the bacterial/fungal interactions (BFIs) that are linked to significant human morbidity and mortality are those between oral microbiota, those between between *Aspergillus fumigatus* and *Pseudomonas aeruginosa* in the lungs, and those with *Clostridioides difficile* in the gut [4].

The PubMed, Scopus, Web of Science, and Google Scholar databases were searched for published structured reviews and articles up to August 2023 using words like bacteria, microbiota, fungi, host interaction, disease, diversity, human, and infectivity. Sixty studies were analyzed.

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DISTRIBUTION OF DIVERSE MICROBIOTA AT VARIOUS BODY SITES

1. Oral cavity

The majority of the oral microbiota is composed of *Streptococcus*; *Lactobacillus; Veillonella*; *Prevotella*; *Staphylococcus*; *Proteobacteria*; *Actinobacteria*; *Fusobacteria*; *Spirochaetes*; *Corynebacterium*; *Pasteurella*; *Neisseria*; *Candida,* of which *C. albicans* is predominant; *Cladosporium*; *Aureobasidium*; *Saccharomyces*; *Aspergillus*; *Fusarium*; *Malassezia*; and *Epicoccum* species [5].

2. Respiratory tract

The respiratory tract's microbial communities are very dynamic. The healthy upper respiratory tract (URT) is populated by *Staphylococcus epidermidis*, *Corynebacterium* spp., *Moraxella* spp., *Propionbacterium* spp., *Staphylococcus aureus* (in approximately 20% of the general population), and *Streptococcus pneumoniae*, along with *Aspergillus* spp., *Penicillium* spp., *Candida* spp., and *Alternaria* spp. In contrast, the paranasal sinuses are normally sterile [6].

The lungs provide a habitat with different development conditions, such as variations in temperature, pH, and oxygen content, in addition to immune cells that produce antimicrobial peptides. The common bacterial microbiota in the healthy lungs include *Streptococcus*, *Prevotella*, *Veillonella*, *Haemophilus*, and *Staphylococcus* spp. [7], as well as *Aspergillus*, *Candida*, *Penicillium*, and *Clavispora* [8].

3. Gastrointestinal tract

The composition of gut microbes depends on several parameters, including food habits, age, medications, pH, smoking, and alcohol consumption. The majority of the gut microbiota belongs to the phyla Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria, particularly the species of *Bacteroides*, *Clostridium*, *Enterococcus faecalis*, *Prevotella*, *Enterobacteriaceae*, *Streptococcus*, *Burkholderia cenocepacia, Salmonella enterica* serovar Typhimurium, and *Bifidobacterium* [9].

Fungi represent 0.1% of all gut pathogens, including *Saccharomyces*, *Cladosporium,* and *Candida,* with *C. albicans*, *Candida glabrata*, *Candida dubliniensis*, and *Candida parapsilosis* being the most dominant species [10].

4. Urinary tract

In contrast to the conventional belief that urine is a sterile fluid, authors have reported *Streptococcus*, *Veillonella*, *Prevotella*, *Bifidobacterium*, *Lactobacillus*, and *Actinomyces* as the dominant urinary microbiota (UM) isolated from asymptomatic persons [11]. Additionally, 30% of women exhibited urinary bladder colonization with *C. albicans* [12].

5. Vagina

The composition of vaginal microflora changes over time in response to numerous host factors, including age, and hormonal changes, as well as contraceptives use, and hygiene habits. Anaerobic lactobacilli are the predominant vaginal microbiota in healthy premenopausal women. Other commensal pathogens include *C. albicans*, *Streptococcus agalactiae, Gardnerella vaginalis*, *Prevotella*, *Ureaplasma*, *Mycoplasma*, *E. faecalis*, and *Escherichia coli* [13].

6. Skin

Propionibacterium spp., *Staphylococcus* spp., *Corynebacterium* spp., *Acinetobacter*, and *Malassezia* are the most established human skin colonizers, followed by *Penicillium, Aspergillus*, *Rhodotorula*, and *Epicoccum* [14]. The distribution of diverse human microbiota is summarized in Fig. 1.

MECHANISMS OF BACTERIAL/FUNGAL INTERACTIONS

Bacteria and fungi can affect each other's survival or virulence using variety of mechanisms, including i) the physical adhesion of bacteria to yeast cell or fungal hyphae through outer membrane proteins, formation of mixed species biofilms or competition for nutrients and attachment sites; ii) signaling-based interaction through quorum sensing (QS) small molecules that affect the morphology and growth of fungi or bacteria and alter their ability to produce infection or invade tissue; iii) modulation of the host environment by metabolic byproducts that change the pH and subsequently stimulate or suppress growth of acid-sensitive microbes; iv) enhancement of metabolic pathways and protein secretion systems; and v) alteration of the host immune response (Fig. 2) [15, 16].

Interestingly, *C. albicans* is the most frequent fungus implicated in mixed BFIs. Although 80% of individuals in the healthy population are colonized with *C. albicans*, severe systemic infection due to *C. albicans* is rare due to the harmony among the human microbiome, which limits the overgrowth of *C. albicans* [17].

C. albicans goes through a number of different morphological changes (yeast, pseudohyphae, chlamydospores, true hyphae). The most virulent is the transition from yeast to the filamentous hyphal form owing to several host-relevant stimuli, such as exposure to serum [18].

The hyphal form is necessary for adherence, tissue invasion and infection, while the yeast morphotype is essential for *C. albicans* commensalism and dissemination. Furthermore, secretion of additional virulence elements, like proteases and cytolytic peptide toxins as candidalysin, is associated with the hyphal form [19].

Commensal and pathogenic bacteria interact with *C. albicans* through a variety of ways. Some bacterial species inhibit *C. albicans* growth, while others release molecules that significantly regulate the yeast-to-hyphal transition in *C. albicans*, as well as biofilm formation. On the other hand, some bacteria enhance the growth of *C. albicans*, which may lead to invasive candidiasis [20].

TYPES OF BACTERIAL/FUNGAL INTERACTIONS IN HEALTH BY ANATOMICAL SITE

1. Oral cavity

Interaction between C. albicans *and* Lactobacillus *spp.*

Lactobacillus spp. produce chemical substances such as lactic acid and cyclic dipeptides that limit *C. albicans* growth and proliferation [21].

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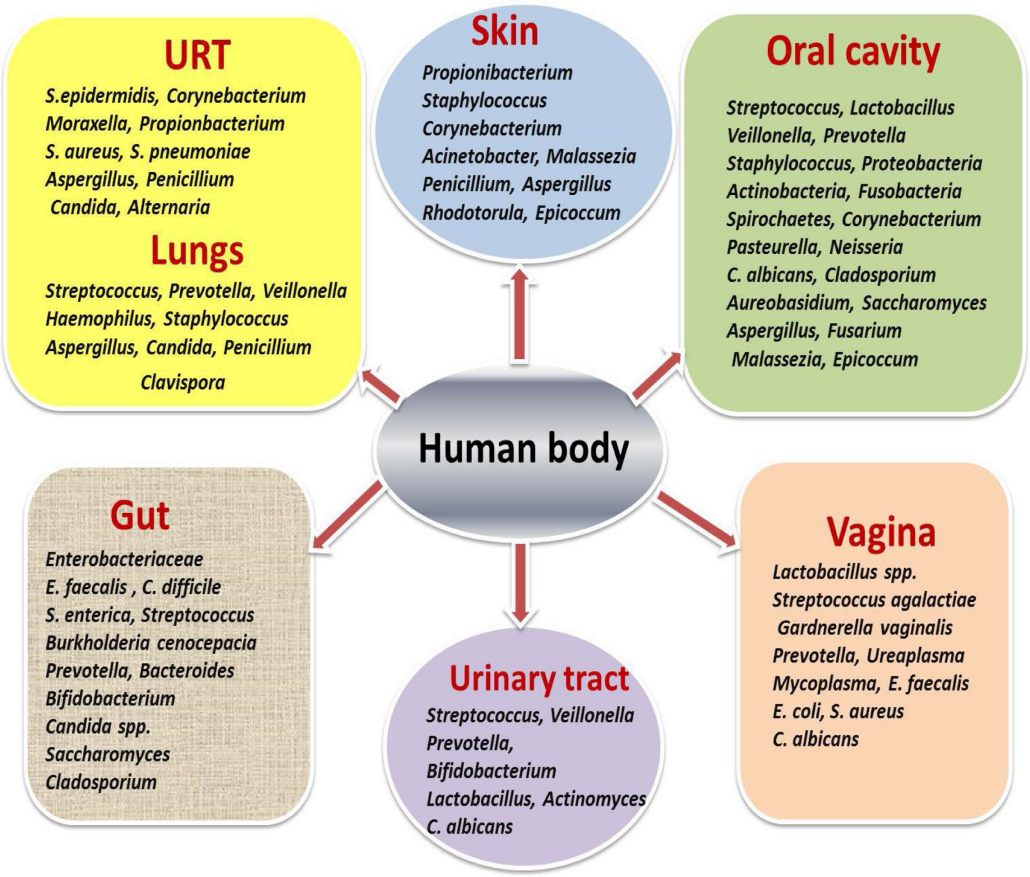

Fig. 1. Graphic illustration of the most commonly identified human microbiota within different body sites.

Relationship between C. albicans *and* Streptococcus mutans

Streptococcus mutans and *C. albicans* interact in a complex way. Firstly, the aggregation and adhesion of *C. albicans* and *S. mutans* is mediated by agglutinin-like sequences (Als1, Als3, Als5) produced by *Candida* and the cell surface polypeptide CshA and antigen I/II salivary adhesins SspA and SspB produced by streptococci [22].

C. albicans secretes the QS molecule farnesol, which at low concentrations promotes the proliferation of *S. mutans* by triggering the expression of the *S. mutans* virulence gene glucosyltransferase B (GtfB). This gene catalyzes the production of extracellular polysaccharides (EPS) and α-glucans and binds to mannans on the surface of *C. albicans,* leading to formation of strong extracellular matrix as well as an increase C. *albicans* resistance to fluconazole. On the other hand, a high farnesol level inhibits the growth of *S. mutans* [23].

Contrarily, *S. mutans* produces the QS molecule diffusible signal factor (DSF), and chemical compounds such as trans-2-decenoic acid, mutanobactin A, and competence-stimulating peptide (CSP), which prevent *C. albicans* hyphal morphogenesis and decrease fungal virulence (Fig. 3) [24].

Interface between C. albicans *and* Streptococcus gordonii

S. gordonii is another *Streptococcus* spp. that interplays synergistically with *C. albicans*. Primarily, *S. gordonii* binds to the host cell receptor on the oral mucosa via cell surface polypeptides; then *C. albicans* selectively binds to salivary basic proline-rich proteins (bPRPs) on the *S. gordonii* surface via specific cell surface glycoprotein and agglutinin-like sequences (Als) [25].

This aggregation generates the QS molecule autoinducing peptide-2 (AI-2) via *S. gordonii*, suppressing *C. albicans* farnesol and promotes *C. albicans* hyphal growth and biofilm formation. In addition, *S. gordonii* produces lactate that is used as a carbon source for *C. albicans*. Similarly, C. *albicans* reduces the oxygen tension level and releases stimulatory molecules to enhance the growth of *S. gordonii* (e.g., polysaccharides) and formation of a fungal-bacterial biofilm surrounded by an extracellular matrix that worsens oral infection and makes it difficult to treat (Fig. 3) [26].

Interaction between C. albicans *and other oral microfloras*

Other oral commensal bacteria, such as *Streptococcus viridans*, *Streptococcus oralis*, *Actinomyces odontolyticus, Actinomyces viscosus, Enterococcus* spp., and *S. aureus*, interact synergistically with *C. albicans* and support the adhesion of *C. albicans* to the buccal mucosa via increased secretion of host proteolytic protein μ calpain that damages E-cadherin and reduces the integrity of the epithelial barriers, causing *C. albicans* tissue invasion and deep organ dissemination as shown in studies using a murine model of infection [27].

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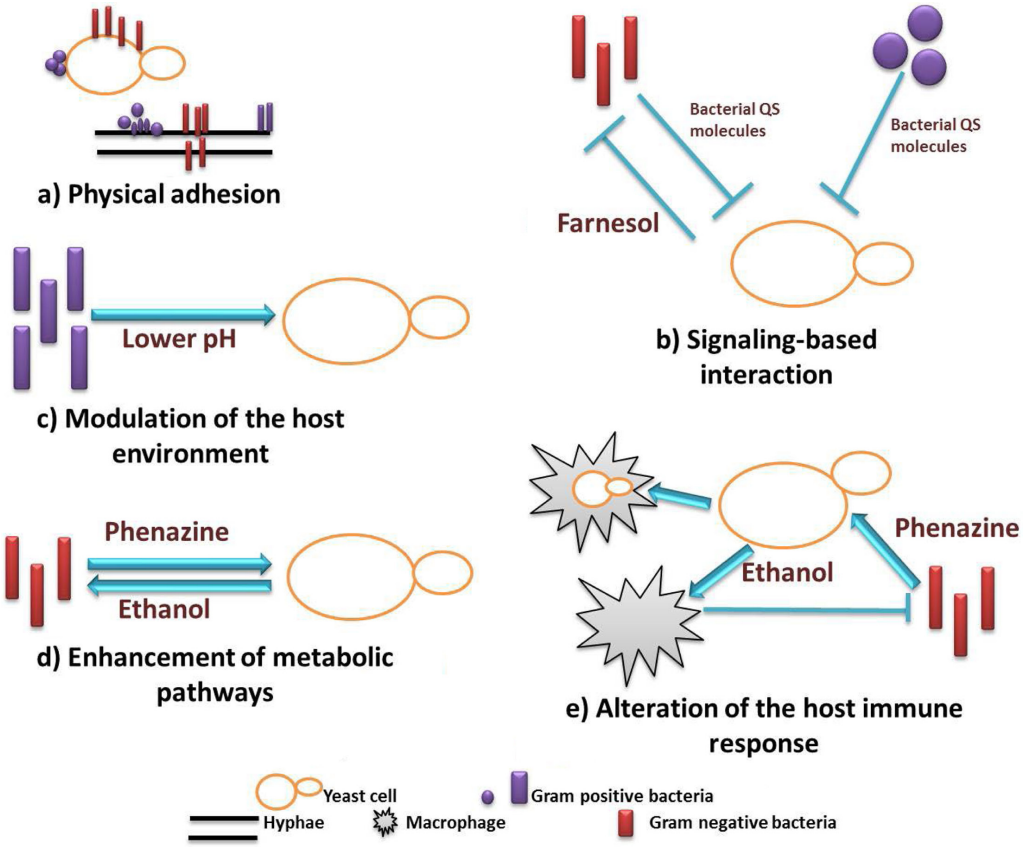

Fig. 2. Various mechanisms of bacterial/fungal interactions.

a) Physical adhesion of bacteria to yeast cell or fungal hyphae through outer membrane proteins. b) Signaling-based interaction: diverse bacteria secrete quorum sensing molecules that impact fungal morphology and biofilm formation. Meanwhile, *C. albicans* (farnesol) suppresses bacteria. c) Modulation of the host environment: bacteria produce lactic acid, which lowers the pH and inhibits *Candida* growth. d) Enhancement of metabolic pathways: bacteria release molecules that enhance metabolic pathways of fungi. e) Alteration of the host immune response: bacteria secrete substances (phenazine) that reduce the escape of *C. albicans* from macrophages, while a *Candida* product (ethanol) impairs the ability of macrophages to remove bacteria.

Aggregatibacter actinomycetemcomitans, *Fusobacterium nucleatum*, *Actinomyces israelii*, *Prevotella nigrescens*, and *Porphyromonas gingivalis* inhibit growth, hyphal transition, and biofilm formation in *C. albicans* [28].

2. Respiratory tract

P. aeruginosa *and* C. albicans *interaction*

Both synergistic and competitive effects can occur in the relationship between *P. aeruginosa* and *C. albicans*. *P. aeruginosa* can physically cling to *C. albicans* filaments in response to the QS molecule N-(3-Oxododecanoyl)-L-homoserine lactone, which generates highly toxic reactive oxygen species (ROS) that inhibit *C. albicans* hyphal development and biofilm formation. Additionally, *P. aeruginosa* produces phenazine chemicals like pyocyanin and hemolytic phospholipase C that have antifungal properties. In contrast, some investigators have described the pseudomonal proteolytic enzyme elastase (LasB; also known as pseudolysin) that enhances the virulence of *C. albicans* in murine pneumonia and burn wound infection models [29].

Furthermore, it is well known that the QS molecule farnesol secreted by *C. albicans* acts as a dual defense mechanism of *C. albicans*; it inhibits hyphal transition in *C. albicans* and maintains itself in the yeast form, which is resistant to killing by phenazine released by *P. aeruginosa*. Additionally, farnesol suppresses pseudomonas quinolone signal (PQS) synthesis, which is correlated with phenazine production [30]; however, increased phenazines synthesis leads to a positive feedback loop that further enhances ethanol secretion by *C. albicans*. Phenazine and ethanol production has an impact on how the host reacts to both pathogens; when *P. aeruginosa* and *C. albicans* co-infect macrophages, phenazines inhibit *C. albicans* filamentation and reduce the escape of *C. albicans* from macrophages, while ethanol impairs the ability of macrophages to remove *P. aeruginosa*, enhancing the colonization of the lungs by the bacterium (Fig. 4) [31].

Interaction between C. albicans *and other bacteria*

C. albicans and *Acinetobacter baumannii* interact negatively with one another. Adhesion of *A. baumannii* to *C. albicans* filaments via outer membrane protein A (OmpA) inhibits *C. albicans* morphogenesis and biofilm formation; meanwhile, the QS molecule farnesol directly inhibits the growth of *A. baumannii* [32].

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The opportunistic pathogen *B. cenocepacia* is mostly acquired from the environment, via hospital devices, or by person-to-person transmission and produces the QS molecule cis-2-dodecenoic acid, which inhibits the initiation of hyphal formation in *C. albicans*; *in vitro* investigations have found that this molecule inhibits adherence of *C. albicans* to urinary catheters. Moreover, *Klebsiella pneumoniae* could inhibit *C. albicans* biofilms [20].

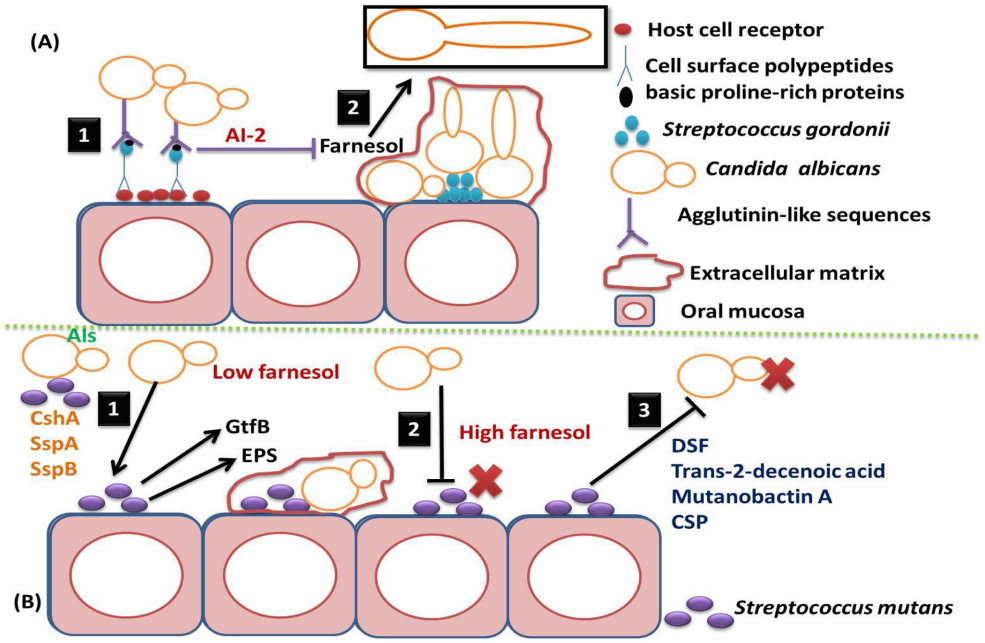

Fig. 3. Interaction between *S. gordonii*, *S. mutans*, and *C. albicans* on the oral mucosa modulates the virulence of the fungus.

a) Interaction between *S. gordonii* and *C. albicans*. 1: Adhesion between *S. gordonii* and *C. albicans* on the oral epithelium. 2: *S. gordonii* produces AI-2, which suppresses *C. albicans* farnesol and promotes *C. albicans* hyphal growth and biofilm formation. b) Interaction between *S. mutans* and *C. albicans*. 1: Aggregation between *S. mutans* and *C. albicans* via adhesions molecules stimulates the secretion of farnesol by *C. albicans*, and the low concentration of farnesol stimulates release of GtfB by *S. mutans*, production of EPS, and formation of strong extracellular matrix, as well as, increases in C. *albicans* resistance. 2: A high farnesol level inhibits the growth of *S. mutans*. 3: Contrarily, *S. mutans* produces DSF, trans-2-decenoic acid, mutanobactin A, and CSP, which block *C. albicans* hyphal morphogenesis.

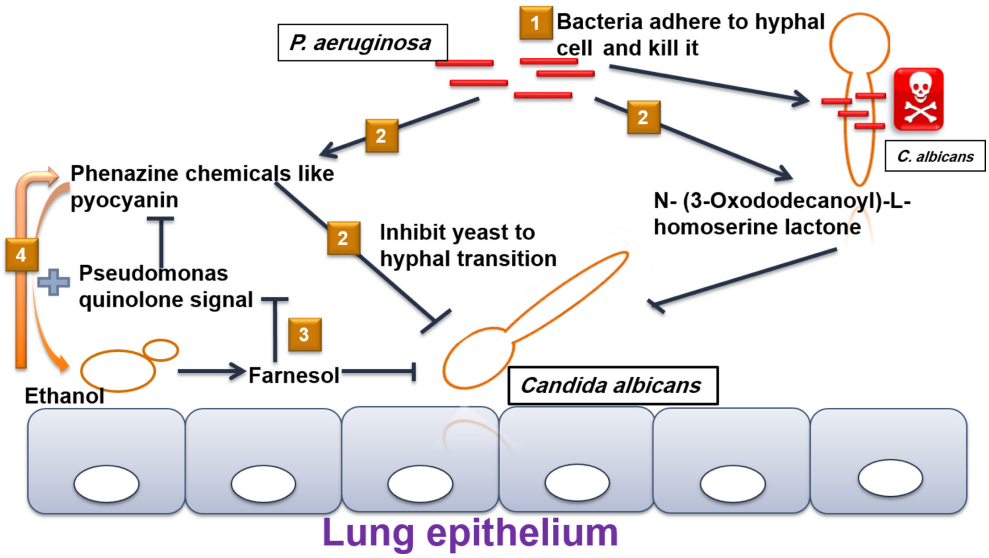

Fig. 4. Interactions between *P. aeruginosa* and *C. albicans* on the lung epithelium.

1) *P. aeruginosa* adheres to hyphal cells and kill them. 2) *P. aeruginosa* secretes the QS molecule N-(3-Oxododecanoyl)-L-homoserine lactone and phenazine compounds, which block the yeast-to-hyphal transition. 3) Farnesol suppresses pseudomonas quinolone signal synthesis, which is linked to phenazine production. 4) Ethanol production by *C. albicans* stimulates phenazine secretion by *P. aeruginosa*, and phenazine then further enhances ethanol production in the fungus through a positive feedback loop.

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Interaction between P. aeruginosa *and* A. fumigatus

The communication between *P. aeruginosa* with *A. fumigatus* is dynamic. On direct contact of *P. aeruginosa* with *A. fumigatus*, the former secretes pyocyanin, pyoverdine, and Qs system LasIR, which inhibit *A. fumigatus* growth and biofilms. Meanwhile, the iron chelating *Pseudomonas* QS molecule PQS has dual actions on *A. fumigatus*; under low iron conditions, it works synergistically with pyoverdine to inhibit biofilm formation in *A. fumigatus*, while under high iron levels, it depends on the *A. fumigatus* iron siderophore, ferricrocin and enhances *A. fumigatus* biofilm formation [33].

Similarly, *P. aeruginosa* produces volatile compounds that stimulate *A. fumigatus* to invade the lung parenchyma when the two organisms are physically separated, but when both come in direct contact, they compete for nutrients, including iron. On the other hand, *A. fumigatus* hyphae secrete gliotoxin, which inhibits the growth of *P. aeruginosa* (Fig. 5) [34].

Interface between Aspergillus *spp. and various bacteria*

The gliotoxin of *A. fumigatus* also inhibits growth and biofilm production in *S. aureus* and *A. baumannii*. Moreover, *A. fumigatus* releases isocyanide compounds that bind copper and exhibit broad-spectrum antimicrobial activity. Otherwise, *S. aureus* and *E. coli* can inhibit *A. fumigatus* conidiation and biofilm maturation via limitation of iron acquisition [35]. In addition, *K. pneumoniae* could inhibit hyphal growth, spore germination, and biofilm formation of several *Aspergillus* spp., like *A. fumigatus*, *Aspergillus terreus*, *Aspergillus niger*, and *Aspergillus flavus in vitro* [36].

C. neoformans *and bacterial interaction*

C. neoformans has numerous virulence traits that protect the ability of the fungus to grow and proliferate at normal body temperature, to form a polysaccharide capsule, to produce melanin pigment, and furthermore to resist phagocytosis by formation of large cryptococcal cells called Titan cells [37].

Various bacteria, such as *Bacillus* spp., *P. aeruginosa*, and *S. aureus*, have inhibitory impacts on *C. neoformans*; *P. aeruginosa* secretes pyocyanin, which inhibits *C. neoformans* growth, while *S. aureus* attaches to the capsule of *C. neoformans* and kills it. In addition, *Bacillus safensis* inhibits melanin production, as well as activates chitinase and blocks capsule formation. In contrast, *A. baumannii* stimulates capsule formation and enhances the growth of *C. neoformans*. Furthermore, *Klebsiella aerogenes* promotes melanin synthesis and increases the virulence of *C. neoformans*, thereby enhancing fungal resistance to external stimuli. Additionally, studies have revealed that *E. coli* and *S. pneumoniae* trigger titan cell formation by *C. neoformans* and help the fungus to evade phagocytosis [38].

3. Gastrointestinal tract

Candida *spp. and* E. coli *interface*

Commensal *E. coli* interacts with *C. albicans* and inhibits fungal colonization. Authors have stated that the anti-candida activity of *E. coli* is due to its lipopolysaccharides, which modulate *C. albicans* growth and biofilm formation. Besides, *E. coli* secretes a soluble factor with bacteriocin-like fungicidal activity that directly kills *C. albicans* [39].

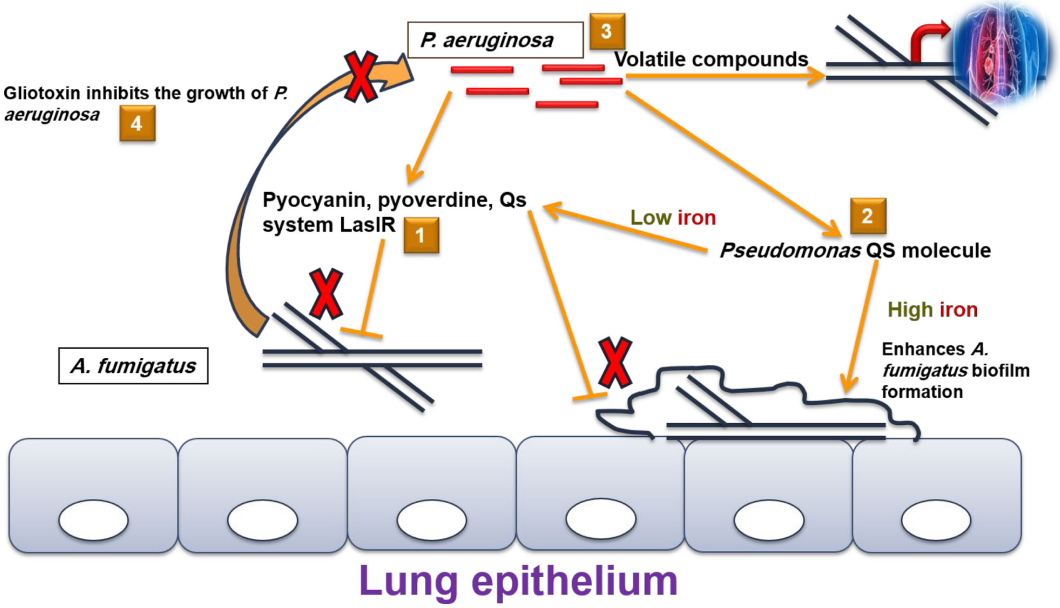

Fig. 5. Interactions between *P. aeruginosa* and *A. fumigatus* on the lung epithelium.

1) *P. aeruginosa* secretes pyocyanin, pyoverdine, and Qs system LasIR, which inhibit *A. fumigatus* growth and biofilms. 2) The *Pseudomonas* QS molecule under low iron conditions inhibits biofilm formation in *A. fumigatus*, while under high iron levels, it enhances *A. fumigatus* biofilm formation. 3) *P. aeruginosa* produces volatile compounds that promote lung invasion by *A. fumigatus*. 4) Moreover, *A. fumigatus* hyphae secrete gliotoxin that inhibits the growth of *P. aeruginosa*.

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Interaction between C. albicans *and* E. faecalis

E. faecalis is another commensal flora that frequently colonizes the large intestine. Prior studies have stated that *E. faecalis* negatively impacts *C. albicans* pathogenicity by producing the bacteriocin EntV and QS molecule Fsr, which expresses GelE (gelatinase, a metalloprotease II) and SerE (serine protease) that reduce *Candida* filamentation [40]. This is in contrast to recent findings that indicated a synergistic interaction between *C. albicans* and *E. faecalis* in the oral and intestinal mucosa. *Enterococcus* reduces the integrity of the epithelial barriers and promotes *C. albicans* invasion and dissemination, in addition to the development of a mixed biofilm on endotracheal tubes in patients with ventilator-associated pneumonia [41].

Interaction between C. albicans *and* S. *Typhimurium*

S. enterica serovar Typhimurium produces the Type III secretion system effector SopB, which inhibits hyphae formation in *C. albicans* and reduces *Candida* virulence [42].

Interaction between C. albicans *and* Clostridioides difficile

Clostridioides difficile (formerly known as *Clostridium difficile*) is an obligate anaerobe that produces *p*-Cresol, which induces the hypha-to-yeast transition, and inhibits the biofilm formation and virulence of *C. albicans;* in contrast, *C. albicans* promotes the growth of *C. difficile* under aerobic conditions by reducing the oxygen tension and antioxidant tyrosol [43].

C. albicans *interaction with Firmicutes and Bacteroidetes*

The Firmicutes and Bacteroidetes in the gut ferment dietary fibers and other polysaccharides, producing short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate, which have a significant role in immune development, control of inflammation, defense against infection, and guarding against CRC. Firmicutes and Bacteroidetes activate intestinal transcription factor HIF-1α, which increases the production of the antimicrobial peptide LL-37, a cathelicidin with anti-*Candida* activity that decreases *C. albicans* colonization; furthermore, they produce butyric acid that inhibits the yeast-to-hyphal transition of *C. albicans* [44].

Relationship between Saccharomyces *spp. and gut bacteria*

Various *in vivo* and *in vitro* studies have revealed that *Saccharomyces cerevisiae* inhibits *E. coli* adhesion and colonization and minimizes the intestinal growth of enterotoxigenic *E. coli* (ETEC). In addition, it reduces *C. difficile* growth [45].

4. Urogenital system

1) Vagina

Interaction of C. albicans *and* Lactobacillus *spp.*

As in the oral cavity, *Lactobacillus* spp. inhibit *Candida* growth in various ways: i) competition for nutrients and attachment sites on the vaginal epithelium; ii) secretion of H_2O_2, cyclic dipeptides, and bacteriocin-like peptides that hinder *C. albicans* growth and proliferation; iii) production of weak organic acids (WOAs), such as lactic acid that lowers the pH, disturbs cell metabolism, inhibits *C. albicans* growth, and suppresses the overgrowth of other facultative anaerobes [46]; iv) release of major secreted protein 1 (Msp1) that acts as a chitinase and breaks down the fungal cell wall; v) synthesis of SCFAs, such as butyric acid, which inhibits the *C. albicans* histone deacetylase enzyme and 1-acetyl-beta-carboline, both inhibiting biofilm formation and hindering the transition of *C. albicans* from the yeast-to-hyphal morphotype [47]; and vi) reduction of the production of the pro-inflammatory cytokines IL-1β, IL-6, and IL-8 (Fig. 6) [48].

Interaction of C. albicans *with* S. agalactiae

S. agalactiae inhibits *C. albicans* hyphal development. Reduced vaginal colonization with *S. agalactiae* was linked with recurrent vulvovaginal candidiasis (VVC) [49].

2) Urinary bladder

C. albicans enhances adherence of *E. coli*, *K. pneumoniae*, and *S. agalactiae* to bladder mucosa, increases colonization and biofilm formation [12].

5. Skin

Interaction between C. albicans *and* Staphylococcus *spp.*

In *C. albicans*/*S. aureus* biofilms, direct contact is mediated by the staphylococcal adhesins FnpB, SasF, and Atl and *Candida* adhesin Als3, and *C. albicans* increases the extracellular pH, which stimulates the production of a major cytotoxic agent (alpha toxin) by *S. aureus*. Moreover, the *C. albicans* QS farnesol increases the production of efflux pumps in *S. aureus*, increasing the resistance of bacteria to antimicrobial agents and hinders wound healing, as found in diabetic foot ulcers [50].

Likewise, *C. albicans* produces prostaglandin E2, which stimulates growth and biofilm formation of *S. aureus*. Furthermore, the fungal cell wall 1, 3, β-glucan released into the extracellular matrix of biofilm covers the bacteria and shields them from antibiotics. Similar to *S. aureus, C. albicans* adhesin Als proteins and *O*-mannosylation play a role in the binding of *S. epidermidis* to the fungus, and co-infection with *C. albicans* led to increased dissemination and tissue invasion of *S. epidermidis* [51].

Interaction between Candida *and* E. coli

In mixed biofilms, *E. coli* negatively affects *Candida*. *E. coli* releases soluble substances with bacteriocin activity that prevent the hyphal transition and biofilm production and kill *Candida* [39]. Medically important bacterial/fungal interactions are summarized in Table 1.

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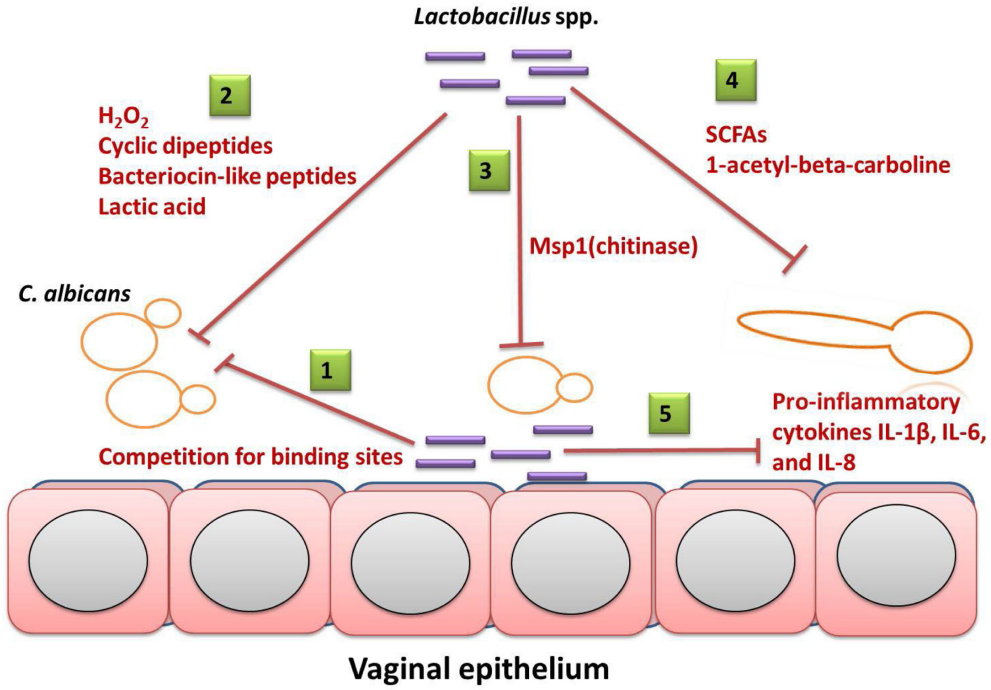

Fig. 6. Interaction between *C. albicans* and *Lactobacillus* spp. on the vaginal epithelium.

1) Competition between *C. albicans* and Lactobacilli for nutrients and attachment sites. 2) Lactobacilli produce H_2O_2, cyclic dipeptides, bacteriocin-like peptides, and lactic acid, which inhibit fungal growth. 3) Lactobacilli release Msp1, which acts as a chitinase, which breaks down the fungal cell wall. 4) Secretion of SCFAs and 1-acetyl-beta-carboline, which hinder the yeast-to-hyphal transition in *C. albicans*. 5) Lactobacilli decrease production of the pro-inflammatory cytokines IL-1β, IL-6, and IL-8.

ROLE OF BACTERIAL/FUNGAL INTERACTIONS IN VARIOUS DISEASES

Unfortunately, not all BFIs are beneficial to the host and reduce fungal load and pathogenesis, and microbial dysbiosis has been implicated in various diseases.

1. Oral diseases

Gingivitis is an oral illness linked to pathogen dysbiosis. It is an inflammatory condition characterized by the formation of dental plaques. If it is not treated, the condition could worsen and progress to chronic periodontitis. *In vitro* cultures have revealed that *C. albicans* and *S. mutans* are the most dominant oral pathogens isolated from dental plaques in several cases, particularly in children suffering from early childhood caries [22].

Additionally, polymicrobial biofilms that develop on dental prostheses, oral candidiasis, periodontitis, and denture stomatitis are associated with co-colonization of *C. albicans* with the oral bacterial microbiota, including *S. gordonii* and *S. oralis*, *A. odontolyticus*, and *A. viscosus*. These commensal bacteria produce chemical signals that increase fungal morphogenesis and biofilm formation in *C. albicans*. Long-term antibiotics use is risk factor of oral dysbiosis as well; a high carbohydrate diet lowers the oral pH and enhances the growth of aciduric bacteria that cause mineral loss and dental caries [52].

2. Lung diseases

While *in vitro* co-cultures have demonstrated that *P. aeruginosa* co-acts antagonistically with fungi, *in vivo* studies have shown that they work together synergistically. Current studies have shed light on microbial imbalance during chronic lung diseases, such chronic obstructive pulmonary disease (COPD), CF, and asthma. The Lungs of CF patients serve as an ideal colonization site for numerous microbes owing to the presence of thick mucus that hinders the penetration of immune cells and antimicrobial substances. Mixed *A. fumigatus* or *C. albicans* colonization with *P. aeruginosa* and *S. aureus* in CF is associated with disease deterioration and worsening of clinical outcome [53].

Airway co-colonization with *C. albicans* and *E. coli*, or *S. aureus*, increases the development of bacterial pneumonia and aggravates the disease severity due to the inhibition of phagocytosis by alveolar macrophages. Moreover, the risk of ventilator-associated pneumonia due to infection by *P. aeruginosa* is markedly greater in patients colonized by *C. albicans*. Additionally, *Aspergillus* colonization of the lower respiratory tract is linked with poor control and reduced lung functions in asthma and allergic bronchopulmonary aspergillosis (ABPA) [25, 34].

3. Gastrointestinal diseases

C. difficile causes gut infection following extended antibiotic therapy manifested by diarrhea, colitis, sepsis, and, in severe cases, death. The presence of *C. albicans* worsens the severity of *C. difficile* infection; studies have found that high *C. albicans* abundance in stool samples is associated with reduced effectiveness of fecal microbiota transplantation (FMT), which is an effective treatment for *C. difficile* infection [54].

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Table 1. Summary of medically important bacterial/fungal interactions at different anatomical body sites

Anatomical site	Bacteria	Fungi	Relationship	Mechanism
Oral cavity	*Lactobacillus* spp.	*C. albicans*	Antagonism	-Releases chemical substances that limit *C. albicans* growth.
	S. mutans	*C. albicans*	Antagonism/ Synergism	- *S. mutans* inhibits *C. albicans* hyphal morphogenesis. - High concentration of *C. albicans* farnesol suppresses *S. mutans* growth and low farnesol levels activates proliferation and biofilm formation in *S. mutans*.
	S. gordonii	*C. albicans*	Synergism	-*S. gordonii* promotes *C. albicans* hyphal growth and biofilm formation, and *C. albicans* enhances growth of *S. gordonii*.
Lungs	*P. aeruginosa*	*C. albicans*	Antagonism/ Synergism	-*P. aeruginosa* produces pyocyanin that inhibits *C. albicans* growth, hyphal morphogenesis. - C. *albicans* produces farnesol and proteins that inhibits *Pseudomonas.* - *C. albicans* releases ethanol that impairs phagocytosis of *Pseudomonas*.
	P. aeruginosa	*A. fumigatus*	Antagonism/ Synergism	- *P. aeruginosa* secretes pyoverdine and pyocyanin that hinder growth of *A. fumigatus*. - *A. fumigatus* secretes gliotoxin that inhibits *P. aeruginosa* growth and biofilm formation. -Pseudomonas under high iron conditions enhances biofilm formation by *A. fumigatus*.
Gut	*E. coli*	*C. albicans*	Antagonism	-Secretes bacteriocin like substance that directly kills the *C. albicans*.
	Enterococcus faecalis	*C. albicans*	Antagonism/ Synergism	-*Enterococcus* directly kills *C. albicans* and prevents hyphal morphogenesis. -As well, it reduces the integrity of the epithelial barriers and promotes *Candida* invasion and dissemination.
	C. difficile	*C. albicans*	Antagonism	-Releases *p*- cresol that directly kills and prevents *C. albicans* hyphal morphogenesis.
	Salmonella enterica serovar Typhimurium	*C. albicans*	Antagonism	- *Salmonella* produces type III secretion system proteins that inhibit hyphae formation in *C. albicans* and reduces its virulence.
Vagina	*Lactobacillus* spp.	*C. albicans*	Antagonism	-Lactobacilli release H_2O_2, SCFAs and lactic acid that inhibit *C. albicans* proliferation. -Lactobacilli secrete Msp1 and 1-acetyl-beta-carboline that break down *Candida* cell wall and inhibit biofilm formation.
	Streptococcus agalactiae	*C. albicans*	Antagonism	-Inhibits *C. albicans* hyphal development.
Urinary tract	*E. coli*	*C. albicans*	Synergism	- *C. albicans* enhances bacterial adhesion and colonization to bladder mucosa.
Skin	*S. aureus*	*C. albicans*	Synergism	- *C. albicans* facilitate tissue penetration and dissemination of *S. aureus*. -*C. albicans* stimulates the production of alpha cytotoxin by *S. aureus*. - Farnesol of *C. albicans* enhances the efflux pump in *S. aureus*, and increase antimicrobial resistance.
	S. epidermidis	*C. albicans*	Synergism	- *Candida* adhesins Als proteins and O-mannosylation led to increased dissemination and tissue invasion of *S. epidermidis.*

SCFAs: short-chain fatty acids.

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Studies have revealed that an imbalance of gut fungi was linked to Crohn's disease and that the gut mycobiota plays a protective function against tissue damage during colitis and viral infection. Despite that, the increased fungal load also poses a risk for disseminated candidiasis. One of the main risk factors for disseminated candidiasis originating from the gut is long-term therapy with broad-spectrum antibiotics because it eradicates the bacteria that control fungal overgrowth; furthermore, butyrate-producing Firmicutes have been described in IBD [26].

Gut co-infection of *C. albicans* and *Serratia marcescens* increases the risk of disseminated abdominal infection due to *S. marcescens,* particularly in immunocompromised patients, which may be complicated with severe sepsis, as C. *albicans* displays a stimulatory effect on *S. marcescens*; additionally, polymicrobial peritonitis caused by *E. coli*, *S. aureus*, and *C. albicans* is linked to higher fatality rates [55].

Dysregulation of gut microbes and overgrowth of pathogens owing to broad-spectrum antibiotics, alcohol, and bad food habits, along with genetic susceptibility, boosts the production of pro-inflammatory cytokines, oxidative factors, and carcinogenic toxins that produce chronic inflammation and disturb the mucosal barrier integrity, increasing the risk of CRC [56].

Genitourinary diseases

Co-infection of the urinary bladder with *C. albicans* and uropathogenic *E. coli*, *K. pneumoniae*, or *S. agalactiae* increases the risk of urinary tract infections (UTIs). *C. albicans* exhibits synergistic action on these bacteria, promotes bacterial adherence to the bladder mucosa, increases colonization and biofilm formation, and reduces bacterial susceptibility to antibiotics. In addition, it has been discovered that imbalance of the UM is responsible for various urological disorders, such as urinary incontinence, interstitial cystitis, overactive bladder, and prostate cancer [12].

Females with reduced vaginal colonization of *Lactobacillus* spp. are at increased risk for developing VVC. *C. albicans* is the predominant cause of VVC, followed by *C. glabrata*, *Candida tropicalis*, and *C. parapsilosis*. Risk factors of VVC include pregnancy, hormone replacement therapy, hygiene practices, immunosuppression, and excess antibiotics use that disturbs the normal protective vaginal microbiota [13].

In addition, *C. albicans*, *E. coli* and *S. agalactiae* vaginal imbalance was found to be concomitant with harmful impacts on the host, such as preterm birth, very low birth weight, and puerperal sepsis [49].

5. Skin diseases

Investigators have described the relation of both the gut microbiota and commensal skin flora with various skin diseases. Numerous SCFAs produced by the gut microflora are essential for the integrity of epithelial barriers, including skin, and several skin diseases have been related to both gut and skin dysbiosis. For instance, acne vulgaris may be linked to *Corynebacterium acnes* strains and a decrease in gut Firmicutes. Likewise, rosacea can be associated with *Helicobacter pylori* infection, and psoriasis is correlated with a higher abundance of skin *Staphylococcus* and *Streptococcus*. Furthermore, atopic dermatitis was found to be related to increased levels of skin *S. aureus* and lower levels of Bacteroidetes and *Bifidobacterium*. Besides, *Escherichia* and an imbalance of gut *Clostridium* were associated with atopic dermatitis in infants [57].

Studies have reported delayed wound healing due to polymicrobial biofilms; moreover, alopecia areata might be due to an imbalance of skin *C. acnes*/*S. epidermidis*. Additionally, dandruff and seborrheic dermatitis have been linked to *Malassezia* spp.; besides, increased *S. aureus* and a reduction of other skin commensals may be correlated with squamous cell carcinoma [58].

6. Systemic infections

Polymicrobial blood stream infections with staphylococci, enterococci, *Klebsiella*, and *Candida*, particularly *C. albicans*, *C. glabrata*, and *C. tropicalis*, were associated with high morbidity and mortality rates [25].

ROLE OF MICROBIOTA AS ANTIMICROBIAL AGENTS

The majority of used antimicrobial agents are non-selective, which may adversely influence the equilibrium of commensal microbiota and may result in the development of antimicrobial resistance. Numerous studies have shed light on the use of commensal pathogens as probiotics in the treatment of diseases caused by microbial dysbiosis, including diarrhea and vaginal candidiasis [46].

Saccharomyces is the only probiotic fungus studied for use in treating intestinal infections brought on by *C. difficile*, ETEC, and *H. pylori*. Protease secreted by *Saccharomyces* breaks down bacterial toxins without harming the microbiota of healthy individuals [45]. Further, FMT is an effective treatment for *C. difficile* infection, recreating a normal gut microbiome [54]. Interestingly, some authors have found that administration of probiotic bacteria could play a protective role against methicillin resistant *S. aureus* (MRSA) and acne vulgaris [57].

Additionally, lactobacilli are frequently utilized as probiotics because of their wide range of antagonistic effects on diverse pathogens. Available freeze-dried lactobacilli can be administered orally or locally via loading on applicators, capsules, and tampons and delivered directly into the vagina. Authors have found that the administration of a probiotic medication in patients with VVC increases the efficacy of azole therapy by reducing fungal colonization, improves burning and itching symptoms, and produces long-lasting treatment [46].

NDV-3A is a newly developed *C. albicans* vaccine based on an anti-virulence strategy using the Als3 adhesin protein, which is essential for *C. albicans* adhesion, invasion, and virulence. It showed excellent efficacy against both systemic and oral candidiasis in mouse models, as well as in recurrent vulvovaginal candidiasis in a double blind, placebo-controlled clinical trial [59].

In a recent study, two new antibacterial agents, complestatin and corbomycin were isolated from anaerobic gut fungi using whole-genome sequencing technology. The two compounds bind to bacterial peptidoglycan and inhibit autolysin activity that is essential for bacterial cell wall remodeling [60].

CONCLUSIONS AND FUTURE OUTLOOK

The fungi, bacteria, and host triangle determines how fungi and bacteria function and how their interactions affect the host. The interactions between bacteria and fungi are dynamic and can be either synergistic or antagonistic. The molecular basis

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of bacterial/fungal interactions is still in its early stages, and further *in vivo* and *in vitro* investigations are required. This is because understanding these connections would help to find new antimicrobial compounds and new therapeutic modalities, as probiotics seem to be a promising alternative as antibacterial and antifungal therapies without hazardous side effects, particularly in the era of antimicrobial resistance. Furthermore, it would help to recognize how commensal pathogens become pathogenic. The human microbiome project may aid us in understanding the physiological effect of microbiota communication on different body systems, and the relations with the occurrence of various pathologies could help to identify people at risk for developing diseases due to an imbalance in their microflora and assist them in re-establishing microbial homeostasis to prevent disease rather than treat it.

AUTHOR CONTRIBUTIONS

The author, R.M.E., completed the data collection, study design, manuscript writing, editing, and final revision of the manuscript.

CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

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REFERENCES

1. d'Enfert C, Kaune AK, Alaban LR, Chakraborty S, Cole N, Delavy M, Kosmala D, Marsaux B, Fróis-Martins R, Morelli M, *et al.* 2021. The impact of the Fungus-Host-Microbiota interplay upon *Candida albicans* infections: current knowledge and new perspectives. FEMS Microbiol Rev 45: fuaa060. [Medline] [CrossRef]
2. Wang F, Xin C, Liu J, Ran Z, Zhao C, Song Z. 2020. Interactions between invasive fungi and symbiotic bacteria. World J Microbiol Biotechnol 36: 137. [Medline] [CrossRef]
3. Santus W, Devlin JR, Behnsen J. 2021. Crossing kingdoms: how the mycobiota and fungal-bacterial interactions impact host health and disease. Infect Immun 89: e00648–e20. [Medline] [CrossRef]
4. Mould DL, Hogan DA. 2021. Intraspecies heterogeneity in microbial interactions. Curr Opin Microbiol 62: 14–20. [Medline] [CrossRef]
5. Le Bars P, Matamoros S, Montassier E, Le Vacon F, Potel G, Soueidan A, Jordana F, de La Cochetière MF. 2017. The oral cavity microbiota: between health, oral disease, and cancers of the aerodigestive tract. Can J Microbiol 63: 475–492. [Medline] [CrossRef]
6. Man WH, de Steenhuijsen Piters WA, Bogaert D. 2017. The microbiota of the respiratory tract: gatekeeper to respiratory health. Nat Rev Microbiol 15: 259–270. [Medline] [CrossRef]
7. Mitchell AB, Glanville AR. 2018. The human respiratory microbiome: implications and impact. Semin Respir Crit Care Med 39: 199–212. [Medline] [CrossRef]
8. Wheeler ML, Limon JJ, Underhill DM. 2017. Immunity to commensal fungi: detente and disease. Annu Rev Pathol 12: 359–385. [Medline] [CrossRef]
9. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, *et al.* 2014. Diet rapidly and reproducibly alters the human gut microbiome. Nature 505: 559–563. [Medline] [CrossRef]
10. Underhill DM, Iliev ID. 2014. The mycobiota: interactions between commensal fungi and the host immune system. Nat Rev Immunol 14: 405–416. [Medline] [CrossRef]
11. Zandbergen LE, Halverson T, Brons JK, Wolfe AJ, de Vos MGJ. 2021. The good and the bad: ecological interaction measurements between the urinary microbiota and uropathogens. Front Microbiol 12: 659450. [Medline] [CrossRef]
12. Shing SR, Ramos AR, Patras KA, Riestra AM, McCabe S, Nizet V, Coady A. 2020. The fungal pathogen *Candida albicans* promotes bladder colonization of group B *Streptococcus*. Front Cell Infect Microbiol 9: 437. [Medline] [CrossRef]
13. De Seta F, Campisciano G, Zanotta N, Ricci G, Comar M. 2019. The vaginal community state types microbiome-immune network as key factor for bacterial vaginosis and aerobic vaginitis. Front Microbiol 10: 2451. [Medline] [CrossRef]
14. Egert M, Simmering R. 2016. The microbiota of the human skin. Adv Exp Med Biol 902: 61–81. [Medline] [CrossRef]
15. MacAlpine J, Robbins N, Cowen LE. 2023. Bacterial-fungal interactions and their impact on microbial pathogenesis. Mol Ecol 32: 2565–2581. [Medline] [CrossRef]
16. Peleg AY, Hogan DA, Mylonakis E. 2010. Medically important bacterial-fungal interactions. Nat Rev Microbiol 8: 340–349. [Medline] [CrossRef]
17. Romo JA, Kumamoto CA. 2020. On commensalism of *Candida*. J Fungi (Basel) 6: 16. [Medline] [CrossRef]
18. Noble SM, Gianetti BA, Witchley JN. 2017. *Candida albicans* cell-type switching and functional plasticity in the mammalian host. Nat Rev Microbiol 15: 96–108. [Medline] [CrossRef]
19. Witchley JN, Penumetcha P, Abon NV, Woolford CA, Mitchell AP, Noble SM. 2019. *Candida albicans* morphogenesis programs control the balance between gut commensalism and invasive infection. Cell Host Microbe 25: 432–443.e6. [Medline] [CrossRef]
20. Nogueira F, Sharghi S, Kuchler K, Lion T. 2019. Pathogenetic impact of bacterial-fungal interactions. Microorganisms 7: 459. [Medline] [CrossRef]
21. Thein ZM, Samaranayake YH, Samaranayake LP. 2006. Effect of oral bacteria on growth and survival of *Candida albicans* biofilms. Arch Oral Biol 51: 672–680. [Medline] [CrossRef]
22. Vílchez R, Lemme A, Ballhausen B, Thiel V, Schulz S, Jansen R, Sztajer H, Wagner-Döbler I. 2010. *Streptococcus mutans* inhibits *Candida albicans* hyphal formation by the fatty acid signaling molecule trans-2-decenoic acid (SDSF). ChemBioChem 11: 1552–1562. [Medline] [CrossRef]
23. Kim D, Sengupta A, Niepa TH, Lee BH, Weljie A, Freitas-Blanco VS, Murata RM, Stebe KJ, Lee D, Koo H. 2017. *Candida albicans* stimulates *Streptococcus mutans* microcolony development via cross-kingdom biofilm-derived metabolites. Sci Rep 7: 41332. [Medline] [CrossRef]
24. Barbosa JO, Rossoni RD, Vilela SF, de Alvarenga JA, Velloso MS, Prata MC, Jorge AO, Junqueira JC. 2016. *Streptococcus mutans* can modulate biofilm formation and attenuate the virulence of *Candida albicans*. PLoS One 11: e0150457. [Medline] [CrossRef]
25. Krüger W, Vielreicher S, Kapitan M, Jacobsen ID, Niemiec MJ. 2019. Fungal-bacterial interactions in health and disease. Pathogens 8: 70. [Medline] [CrossRef]
26. Morales DK, Hogan DA. 2010. *Candida albicans* interactions with bacteria in the context of human health and disease. PLoS Pathog 6: e1000886. [Medline] [CrossRef]
27. Xu H, Sobue T, Bertolini M, Thompson A, Dongari-Bagtzoglou A. 2016. *Streptococcus oralis* and *Candida albicans* synergistically activate μ-Calpain to degrade E-cadherin from oral epithelial junctions. J Infect Dis 214: 925–934. [Medline] [CrossRef]
28. Bachtiar EW, Bachtiar BM, Jarosz LM, Amir LR, Sunarto H, Ganin H, Meijler MM, Krom BP. 2014. AI-2 of *Aggregatibacter actinomycetemcomitans* inhibits *Candida albicans* biofilm formation. Front Cell Infect Microbiol 4: 94. [Medline] [CrossRef]
29. Bandara HMHN, Wood DLA, Vanwonterghem I, Hugenholtz P, Cheung BPK, Samaranayake LP. 2020. Fluconazole resistance in *Candida albicans* is induced by *Pseudomonas aeruginosa* quorum sensing. Sci Rep 10: 7769. [Medline] [CrossRef]
30. Lopez-Medina E, Fan D, Coughlin LA, Ho EX, Lamont IL, Reimmann C, Hooper LV, Koh AY. 2015. *Candida albicans* inhibits *Pseudomonas aeruginosa* virulence through suppression of pyochelin and pyoverdine biosynthesis. PLoS Pathog 11: e1005129. [Medline] [CrossRef]
31. Morales DK, Grahl N, Okegbe C, Dietrich LE, Jacobs NJ, Hogan DA. 2013. Control of *Candida albicans* metabolism and biofilm formation by *Pseudomonas aeruginosa* phenazines. MBio 4: e00526–e12. [Medline] [CrossRef]
32. Gaddy JA, Tomaras AP, Actis LA. 2009. The *Acinetobacter baumannii* 19606 OmpA protein plays a role in biofilm formation on abiotic surfaces and in the interaction of this pathogen with eukaryotic cells. Infect Immun 77: 3150–3160. [Medline] [CrossRef]
33. Nazik H, Sass G, Ansari SR, Ertekin R, Haas H, Déziel E, Stevens DA. 2020. Novel intermicrobial molecular interaction: *Pseudomonas aeruginosa* Quinolone Signal (PQS) modulates *Aspergillus fumigatus* response to iron. Microbiology (Reading) 166: 44–55. [Medline] [CrossRef]
34. Briard B, Mislin GLA, Latgé JP, Beauvais A. 2019. Interactions between *Aspergillus fumigatus* and pulmonary bacteria: current state of the field, new data, and future perspective. J Fungi (Basel) 5: 48. [Medline] [CrossRef]
35. Raffa N, Won TH, Sukowaty A, Candor K, Cui C, Halder S, Dai M, Landero-Figueroa JA, Schroeder FC, Keller NP. 2021. Dual-purpose isocyanides produced by *Aspergillus fumigatus* contribute to cellular copper sufficiency and exhibit antimicrobial activity. Proc Natl Acad Sci USA 118: e2015224118. [Medline] [CrossRef]
36. Nogueira MF, Pereira L, Jenull S, Kuchler K, Lion T. 2019. *Klebsiella pneumoniae* prevents spore germination and hyphal development of *Aspergillus* species. Sci Rep 9: 218. [Medline] [CrossRef]
37. Iyer KR, Revie NM, Fu C, Robbins N, Cowen LE. 2021. Treatment strategies for cryptococcal infection: challenges, advances and future outlook. Nat Rev Microbiol 19: 454–466. [Medline] [CrossRef]
38. Mayer FL, Kronstad JW. 2019. The spectrum of interactions between *Cryptococcus neoformans* and bacteria. J Fungi (Basel) 5: 31. [Medline] [CrossRef]

39. Cabral DJ, Penumutchu S, Norris C, Morones-Ramirez JR, Belenky P. 2018. Microbial competition between *Escherichia coli* and *Candida albicans* reveals a soluble fungicidal factor. Microb Cell 5: 249–255. [Medline] [CrossRef]
40. Graham CE, Cruz MR, Garsin DA, Lorenz MC. 2017. *Enterococcus faecalis* bacteriocin EntV inhibits hyphal morphogenesis, biofilm formation, and virulence of *Candida albicans*. Proc Natl Acad Sci USA 114: 4507–4512. [Medline] [CrossRef]
41. Adair CG, Gorman SP, Feron BM, Byers LM, Jones DS, Goldsmith CE, Moore JE, Kerr JR, Curran MD, Hogg G, *et al.* 1999. Implications of endotracheal tube biofilm for ventilator-associated pneumonia. Intensive Care Med 25: 1072–1076. [Medline] [CrossRef]
42. Bratburd JR, Keller C, Vivas E, Gemperline E, Li L, Rey FE, Currie CR. 2018. Gut microbial and metabolic responses to *Salmonella enterica* serovar Typhimurium and *Candida albicans*. MBio 9: e02032–e18. [Medline] [CrossRef]
43. Kumamoto CA, Gresnigt MS, Hube B. 2020. The gut, the bad and the harmless: *Candida albicans* as a commensal and opportunistic pathogen in the intestine. Curr Opin Microbiol 56: 7–15. [Medline] [CrossRef]
44. Manor O, Dai CL, Kornilov SA, Smith B, Price ND, Lovejoy JC, Gibbons SM, Magis AT. 2020. Health and disease markers correlate with gut microbiome composition across thousands of people. Nat Commun 11: 5206. [Medline] [CrossRef]
45. Roussel C, Sivignon A, de Vallée A, Garrait G, Denis S, Tsilia V, Ballet N, Vandekerckove P, Van de Wiele T, Barnich N, *et al.* 2018. Anti-infectious properties of the probiotic *Saccharomyces cerevisiae* CNCM I-3856 on enterotoxigenic *E. coli* (ETEC) strain H10407. Appl Microbiol Biotechnol 102: 6175–6189. [Medline] [CrossRef]
46. Zhang Z, Lv J, Pan L, Zhang Y. 2018. Roles and applications of probiotic *Lactobacillus* strains. Appl Microbiol Biotechnol 102: 8135–8143. [Medline] [CrossRef]
47. Allonsius CN, Vandenheuvel D, Oerlemans EFM, Petrova MI, Donders GGG, Cos P, Delputte P, Lebeer S. 2019. Inhibition of *Candida albicans* morphogenesis by chitinase from *Lactobacillus rhamnosus* GG. Sci Rep 9: 2900. [Medline] [CrossRef]
48. Santos CMA, Pires MCV, Leão TL, Silva AKS, Miranda LS, Martins FS, Silva AM, Nicoli JR. 2018. Anti-inflammatory effect of two *Lactobacillus* strains during infection with *Gardnerella vaginalis* and *Candida albicans* in a HeLa cell culture model. Microbiology (Reading) 164: 349–358. [Medline] [CrossRef]
49. Yu XY, Fu F, Kong WN, Xuan QK, Wen DH, Chen XQ, He YM, He LH, Guo J, Zhou AP, *et al.* 2018. *Streptococcus agalactiae* inhibits *Candida albicans* hyphal development and diminishes host vaginal mucosal TH17 response. Front Microbiol 9: 198. [Medline] [CrossRef]
50. Todd OA, Fidel PL Jr, Harro JM, Hilliard JJ, Tkaczyk C, Sellman BR, Noverr MC, Peters BM. 2019. *Candida albicans* augments *Staphylococcus aureus* virulence by engaging the staphylococcal agr quorum sensing system. MBio 10: e00910–e00919. [Medline] [CrossRef]
51. Rogiers O, Holtappels M, Siala W, Lamkanfi M, Van Bambeke F, Lagrou K, Van Dijck P, Kucharíková S. 2018. Anidulafungin increases the antibacterial activity of tigecycline in polymicrobial *Candida albicans*/*Staphylococcus aureus* biofilms on intraperitoneally implanted foreign bodies. J Antimicrob Chemother 73: 2806–2814. [Medline] [CrossRef]
52. Satala D, Gonzalez-Gonzalez M, Smolarz M, Surowiec M, Kulig K, Wronowska E, Zawrotniak M, Kozik A, Rapala-Kozik M, Karkowska-Kuleta J. 2022. The Role of *Candida albicans* virulence factors in the formation of multispecies biofilms with bacterial periodontal pathogens. Front Cell Infect Microbiol 11: 765942. [Medline] [CrossRef]
53. Blomquist A, Inghammar M, Al Shakirchi M, Ericson P, Krantz C, Svedberg M, Lindblad A, Påhlman LI. 2022. Persistent *Aspergillus fumigatus* infection in cystic fibrosis: impact on lung function and role of treatment of asymptomatic colonization-a registry-based case-control study. BMC Pulm Med 22: 263. [Medline] [CrossRef]
54. Zuo T, Wong SH, Cheung CP, Lam K, Lui R, Cheung K, Zhang F, Tang W, Ching JYL, Wu JCY, *et al.* 2018. Gut fungal dysbiosis correlates with reduced efficacy of fecal microbiota transplantation in *Clostridium difficile* infection. Nat Commun 9: 3663. [Medline] [CrossRef]
55. Esher SK, Fidel PL Jr, Noverr MC. 2019. *Candida*/staphylococcal polymicrobial intra-abdominal infection: pathogenesis and perspectives for a novel form of trained innate immunity. J Fungi (Basel) 5: 37. [Medline] [CrossRef]
56. Genua F, Raghunathan V, Jenab M, Gallagher WM, Hughes DJ. 2021. The role of gut barrier dysfunction and microbiome dysbiosis in colorectal cancer development. Front Oncol 11: 626349. [Medline] [CrossRef]
57. De Pessemier B, Grine L, Debaere M, Maes A, Paetzold B, Callewaert C. 2021. Gut-skin axis: current knowledge of the interrelationship between microbial dysbiosis and skin conditions. Microorganisms 9: 353. [Medline] [CrossRef]
58. Chen P, He G, Qian J, Zhan Y, Xiao R. 2021. Potential role of the skin microbiota in Inflammatory skin diseases. J Cosmet Dermatol 20: 400–409. [Medline] [CrossRef]
59. Edwards JE Jr, Schwartz MM, Schmidt CS, Sobel JD, Nyirjesy P, Schodel F, Marchus E, Lizakowski M, DeMontigny EA, Hoeg J, *et al.* 2018. A fungal immunotherapeutic vaccine (NDV-3A) for treatment of recurrent vulvovaginal candidiasis-a phase 2 randomized, double-blind, placebo-controlled trial. Clin Infect Dis 66: 1928–1936. [Medline] [CrossRef]
60. Culp EJ, Waglechner N, Wang W, Fiebig-Comyn AA, Hsu YP, Koteva K, Sychantha D, Coombes BK, Van Nieuwenhze MS, Brun YV, *et al.* 2020. Evolution-guided discovery of antibiotics that inhibit peptidoglycan remodelling. Nature 578: 582–587. [Medline] [CrossRef]

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