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Ascomycetes yeasts: The hidden part of human microbiome

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Abstract

The fungal component of the microbiota, the mycobiota, has been neglected for a long time due to its poor richness compared to bacteria. Limitations in fungal detection and taxonomic identification arise from using metagenomic approaches, often borrowed from bacteriome analyses. However, the relatively recent discoveries of the ability of fungi to modulate the host immune response and their involvement in human diseases have made mycobiota a fundamental component of the microbial communities inhabiting the human host, deserving some consideration in host–microbe interaction studies and in metagenomics. Here, we reviewed recent data on the identification of yeasts of the Ascomycota phylum across human body districts, focusing on the most representative genera, that is, *Saccharomyces* and *Candida*. Then, we explored the key factors involved in shaping the human mycobiota across the lifespan, ranging from host genetics to environment, diet, and lifestyle habits. Finally, we discussed the strengths and weaknesses of culture-dependent and independent methods for mycobiota characterization. Overall, there is still room for some improvements, especially regarding fungal-specific methodological approaches and bioinformatics challenges, which are still critical steps in mycobiota analysis, and to advance our knowledge on the role of the gut mycobiota in human health and disease.

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1 | INTRODUCTION

Human microbiota is a complex ecosystem consisting of microorganisms from all kingdoms of life, namely bacteria, archaea, unicellular eukaryotes, including yeasts and protozoa, multicellular eukaryotes, such as fungi and helminths, and viruses (Norman et al., 2014; Virgin, 2014). Despite fungi and yeasts having been detected in human stool samples

as far back as 1917, and since the mid-20th century the presence of yeasts in the human intestine was proposed to have a saprotrophic role, the majority of microbiota studies have focused mainly on bacterial communities (Gorbach et al., 1967; Gumbo et al., 1999). The fungal component of the microbiota, the mycobiota, has been neglected for a long time, mostly because of its poor abundance compared to bacteria (Ghannoum et al., 2010; Iliev et al., 2012). In the human gut, fungi are estimated to make up approximately 0.1% of the total microorganisms (Qin et al., 2010), yet this assessment might underestimate their actual richness. To date, the mycobiota has gained recognition as a fundamental part of the microbial communities inhabiting several human body districts, due to its potential involvement in the etiology of several diseases, especially gut-associated conditions (Ott et al., 2008; Sokol et al., 2017; Underhill & Iliev, 2014), and due to the ability of fungi to modulate the host immune response (di Paola et al., 2020; Iliev et al., 2012).

Almost 50 years of culture-based and a decade of metagenomic-based studies have outlined an overview of the fungal phyla within the human mycobiota, and all the recent reviews on the mycobiota composition agree that the most represented yeasts are *Candida* and *Saccharomyces* genera belonging to *Ascomycota* phylum (Begum et al., 2022; Belvoncikova et al., 2022; Iliev & Leonardi, 2017; Limon et al., 2017; Runge & Rosshart, 2021; Underhill & Iliev, 2014). This review is a survey of the current literature on (i) the human mycobiota composition, focusing on Ascomycetes yeasts, (ii) the factors that shape the mycobiota during the human lifespan, and (iii) an introduction to methods and technologies for mycobiota characterization, highlighting strengths and limitations.

2 | THE HUMAN MYCOBIOTA: RICHNESS AND DIVERSITY IN THE HUMAN BODY SITES

While the bacterial microbiota is relatively stable over time, evidence suggests that the mycobiota is highly variable not only between individuals, but also within the same person during the lifespan (Findley et al., 2013; Hallen-Adams & Suhr, 2017; Scanlan & Marchesi, 2008; Strati, di Paola, et al., 2016). Moreover, one of the first studies on the characterization of mycobiota in the healthy human gut showed marked differences in richness and diversity according to gender and age, with younger individuals and females having a higher fungal richness compared to adults and male subjects, respectively (Strati, di Paola, et al., 2016). For instance, *Basidiomycota* (species belonging to the genus *Malassezia*) colonize preferentially the skin surfaces of both males and females, while the female reproductive tract and the intestinal tract are mostly inhabited by *Ascomycota*, especially species belonging to the genus *Candida*. Additionally, several studies showed the presence of fungal communities in breast milk suggesting a specific mother-offspring transmission of the mycobiome (Boix-Amorós et al., 2019; Fiers et al., 2020; Saxena et al., 2018; Shivaji et al., 2022). Here, we reviewed the current knowledge about the *Ascomycota* yeasts residents in the most characterized human body districts, such as the oral tract, lungs, gut, genitourinary tract, and skin (Figure 1).

2.1 | Oral tract

The mouth is one of the first human body sites where the presence of Ascomycetes yeasts was described more than 60 years ago (Krasner et al., 1956). Since fungi are difficult to grow in ordinary laboratory culture media, some uncultivable species have eluded detection, and the predominant species belonging to the genus *Candida* have stolen the spotlight for decades (Diaz et al., 2017; Young et al., 1951). Subsequently, the implementation of metagenomics through next-generation sequencing (NGS) techniques has shown the presence of a manifold oral fungal community (Bandara et al., 2019; Ghannoum et al., 2010). Other studies have shown that, while bacterial diversity in the oral cavity is one of the highest in the human body sites, the mycobiota of a single individual is relatively stable over time, but with higher inter-individual variations. This result suggests, on one hand, a core fungal community and, on the other hand, a more variable group of fungi in the oral cavity (Diaz & Dongari-Bagtzoglou, 2021; Monteiro-da-Silva et al., 2014). To date, oral mycobiota studies suggested that *Candida* is the most represented fungal genus within the *Ascomycota* phylum (Charlson et al., 2012; Diaz et al., 2017), but other Ascomycetes yeasts genera, namely *Aureobasidium*, *Saccharomyces*, and *Pichia*, were described as part of oral mycobiota (Auchtung et al., 2018; Ghannoum et al., 2010; Khadija et al., 2021; Monteiro-da-Silva et al., 2014; Stehlikova et al., 2019). Two different studies on saliva and oral mucosa samples suggested the existence of two possible community types, based on the abundance of *Candida* (mycotype 1) and *Malassezia* species (mycotype 2), respectively (Abusleme et al., 2018; Hong, Hoare, et al., 2020). Moreover, each mycotype seems to be associated with specific clinical and bacteriome profiles. Besides these two genera, metagenomic studies suggest that the rest of the fungal diversity is almost certainly acquired from the environment, mostly from
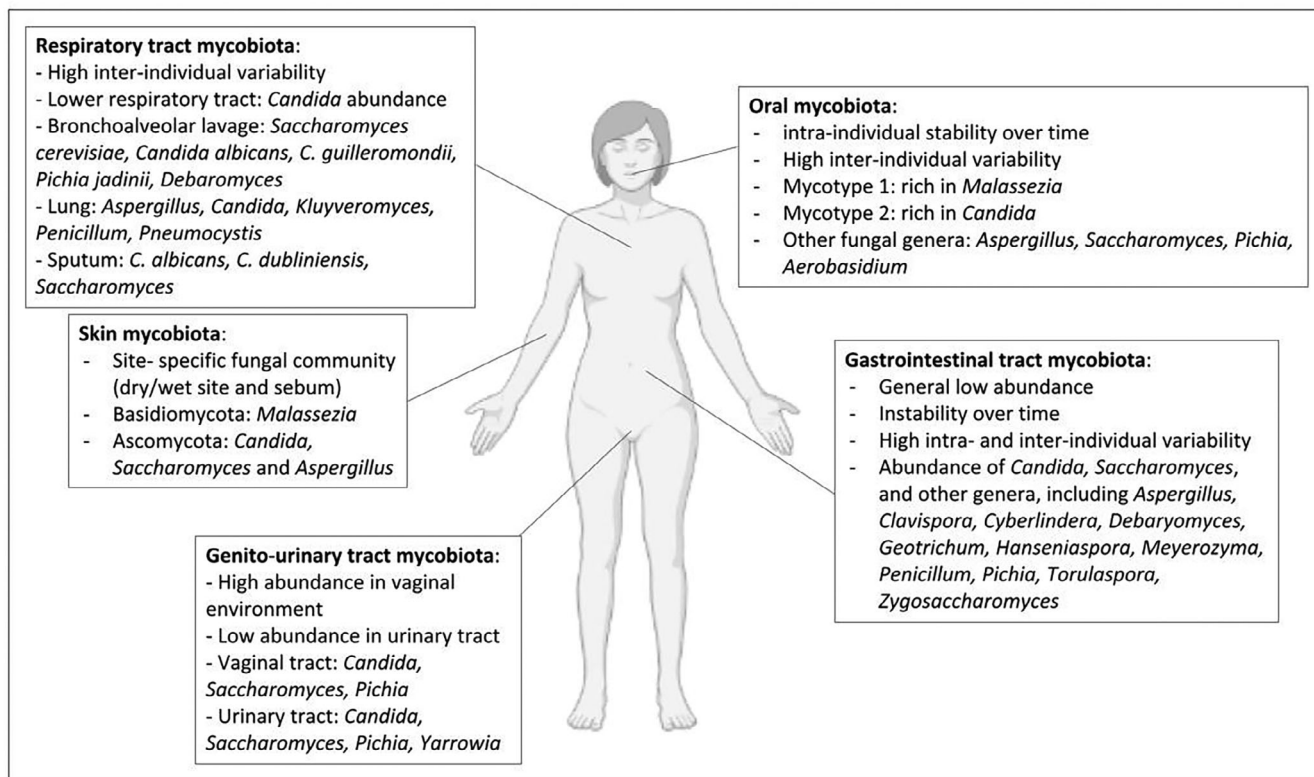
FIGURE 1 Overview of mycobiota composition in the major studied human body sites. In each human anatomical district, inter- and intra-individual fungal variability and the identified Ascomycetes fungal populations, in health conditions, are described.

ingested food (Diaz & Dongari-Bagtzoglou, 2021). The first evidence of a pathogenic oral mycobiota comes from studies on HIV-positive (HIV+) patients. These patients can frequently develop pharyngeal candidiasis, where the overgrowth of *Candida albicans* leads to an opportunistic infection (Klein et al., 1984). It is well known that, under certain conditions, *C. albicans* can shift from commensal to pathogenic status. In the oral tract, the balance of this transition is regulated not only by the host immune system (Cassone & Cauda, 2012), but also by the fungal–fungal interaction. Specifically, in oral mycobiota of HIV+ patients, an inverse correlation was observed between the pathogenicity of *C. albicans* and the abundance of *Pichia* species. The inhibitory effects of *Pichia* on *Candida* could be due to the secretion of a mycotoxin (Mukherjee et al., 2014). Numerous other studies have suggested a role for the genus *Candida* in oral dysbiosis and, in general, in disease. Increased abundance of *C. albicans* and *C. dubliniensis* species is correlated with dental caries in early childhood (Ghasempour et al., 2011; Kneist et al., 2015). Increased abundance of *C. glabrata* resulted in tongue infections and the interactions between *C. glabrata* and hyphae of *C. albicans* established oropharyngeal candidiasis, as well as an abundance of *C. parapsilosis*, *C. tropicalis*, and *C. crusei* (Tati et al., 2016). Significantly higher abundances of the genus *Candida* were observed in patients with erosive oral lichen planus (Y. Li et al., 2019). In a recent study alteration of the oral mycobiota caused by smoking tobacco showed a decreased oral fungal diversity and an increase of the *Pichia* genus correlated with the severity of oral lesions (Sajid et al., 2022).

2.2 | Respiratory tract

Despite the respiratory tract being constantly exposed to environmental and airborne fungi and being inevitably in contact with oral mycobiota (Nguyen et al., 2015; van Woerden et al., 2013), in healthy individuals, lungs have been considered sterile until less than 30 years ago (Cabello et al., 1997). Bacterial colonization was thought to occur only during disease (Marsland & Gollwitzer, 2014). Before culture-independent approaches, fungal communities have been studied only in lower respiratory tract (LRT) diseases, revealing the presence of multiple *Candida* species (Baum, 1960; Corley et al., 1997; el-Ebiary et al., 1997; Meersseman et al., 2009). During the NGS era, few studies investigated the mycobiota

of the respiratory tract in health status. However, these studies reached a consensus on three main points: (i) in health conditions, fungi are present in the human respiratory tract; (ii) in the respiratory tract, fungi are highly variable between individuals; and (iii) many diseases affecting lungs are associated to a decreased fungal diversity (Nguyen et al., 2015; Tipton et al., 2017).

To date, the published literature showed a clearer overview of predominant fungal species in the different sites of the respiratory tract, mainly belonging to *Ascomycota* and *Basidiomycota* phyla. From bronchoalveolar lavage samples, Ascomycetes yeasts, such as *Saccharomyces cerevisiae*, *Candida albicans*, *Meyerozyma guilliermondii* (*Candida guilliermondii*), *Pichia jadinii*, and *Debaryomyces* spp. were found (Charlson et al., 2012; Cui et al., 2015; Martinsen et al., 2021). In the lungs, *Candida* spp., *Kluyveromyces* spp., and *Pneumocystis* spp. were predominant (Charlson et al., 2012; Delhaes et al., 2012). In sputum, *Candida albicans*, *Candida dubliniensis*, and *Saccharomyces* spp. were also identified (Ali et al., 2019). In patients with noninflammatory respiratory tract disorders, a recent study found no substantial differences in the core lung mycobiota (mainly characterized by *Malassezia*, *Candida*, and *Cryptococcus* genera) with respect to previous studies, except for a lower abundance of *Candida* spp. (including the absence of *C. albicans*) and a higher diversity of the total oral microbiota (Rubio-Portillo et al., 2020). The observed discrepancies among studies are probably due to the type of collected biological samples. The predominance of *Candida* spp., as observed in some studies, could be explained by the frequent use of sputum as a representative sample of the LRT condition (Aliouat-Denis et al., 2014; Delhaes et al., 2012; Soret et al., 2020; Willger et al., 2014), while these types of samples would carry fungi for the upper respiratory tract, where *Candida* spp. is prevalent. Regarding the differences in microbiota diversity of the entire lungs, it is known that inflammation is associated with reduced diversity of the microbial community compared to a noninflammatory disease condition (Enaud et al., 2018; Huffnagle & Noverr, 2013; Richardson et al., 2019; Soret et al., 2020). An overview of the culture-independent studies (Krause et al., 2017) on mycobiota of the lower respiratory tract confirms that the genus *Candida* is predominant in most of the studies on several conditions, such as cystic fibrosis, lung transplant, HIV-infected, intensive care unit (ICU), bronchiectasis, asthma, and immunocompromised patients (Bittinger et al., 2014; Bousbia et al., 2012; Charlson et al., 2012; Cui et al., 2014, 2015; Kramer et al., 2015; Krause et al., 2017; Mac Aogáin et al., 2018; van Woerden et al., 2013; Willger et al., 2014; Zinter et al., 2019).

2.3 | Gastrointestinal tract

The gastrointestinal tract (GIT) is the most studied human body site concerning the characterization of microbial communities. Multiple studies across years have demonstrated that fungi are normal inhabitants of the GIT (David et al., 2014; Dollive et al., 2013; Hoffmann et al., 2013; Hube, 2004; Iliev et al., 2012; Nilsson et al., 2006; Scupham et al., 2006; Underhill & Iliev, 2014). The presence of fungal communities has been detected in the gut of at least 70% of healthy adults (Raimondi et al., 2019; Schulze & Sonnenborn, 2009). However, there is not a broad consensus in defining a healthy gut mycobiota. Multiple factors, including low abundance and diversity of fungi in the gut, temporal instability of mycobiota across the lifespan, and high variability of both inter- and intra-individual across time affect the gut mycobiota composition (Hallen-Adams & Suhr, 2017; Nash et al., 2017). Fungi represent only 0.1% of the total gut microorganisms (Arumugam et al., 2011; Qin et al., 2010). The concentration of fungi along the gut seems to be relatively stable, with an average of 10^6 cells per gram (Huseyin, O'Toole, et al., 2017; Sender et al., 2016), compared to the bacterial community, whose concentration increases from the stomach to the colon (Donaldson et al., 2016; Jiang et al., 2017). Therefore, the ratio between fungi and bacteria might be higher in the upper GIT than in the colon (Richard & Sokol, 2019). Several studies showed that the biodiversity of human mycobiota is also lower and characterized by greater unevenness than the bacterial microbiota (Breau et al., 2022; Nash et al., 2017; Qin et al., 2010; Raimondi et al., 2019). Moreover, the fungal biodiversity seems to increase from the stomach to the lower GIT (Hallen-Adams & Suhr, 2017). Fungi also produce a wide range of metabolites with the potential to affect host and intercellular communication (Enaud et al., 2018). Thus, gut mycobiota could play a key role in both host's homeostasis and disease, as already described for the bacteriome (Leonardi et al., 2022; Mims et al., 2021; Sam et al., 2017).

Historically, mycobiota studies were based on in vitro cultures (Finegold et al., 1974), but the development of culture-independent methods allowed the discovery of a much more diverse fungal community due to unculturable fungal species (Browne et al., 2016; Gouba et al., 2013), both in health and disease (Huseyin, O'Toole, et al., 2017).

One of the first studies that relied on culture-independent methods to assess the composition of human gut mycobiota detected fungal species in 88% of the sampled individuals (Scanlan & Marchesi, 2008). The first comprehensive culture-independent study of a large cohort of individuals performed by means of both targeted and untargeted

metagenomic approaches has been conducted within the Human Microbiome Project (HMP; Nash et al., 2017). Results from 370 stool samples confirmed the lower diversity of the fungal community compared to bacteria, and the high variability of both inter- and intra-volunteer. Moreover, in these samples, yeast represented 8 of the 15 most abundant found genera. *Ascomycota* was the predominant phylum, with a prevalence of the genera *Saccharomyces* and *Candida* (found in 96.8% and 80.8% of the samples, respectively), followed by *Basidiomycota* (70% and 30%, respectively). Other findings, both in mice (Dollive et al., 2013) and in humans (Underhill & Iliev, 2014), showed that the mycobiota of a single subject is no more similar to itself over time compared with that of another individual. However, several fungal species persist across the majority of samples from different individuals. These clues suggest that a human core gut mycobiota may exist. The fungal species characterizing the core mycobiota were already identified in previous studies through culture-dependent methods (Agirbasli et al., 2005; Gouba et al., 2013, 2014a; Scanlan & Marchesi, 2008; Strati, di Paola, et al., 2016) and the results of the HMP project studies confirmed them. Ascomycetes yeasts are the predominant fungi, especially the genera *Candida* and *Saccharomyces* (Borges et al., 2018; Botschuijver et al., 2017; Y. Chen et al., 2011; Hamad et al., 2012; Kabwe et al., 2020; Motooka et al., 2017; Pandey et al., 2012). Other ascomycetes yeasts described in human gut mycobiota belonged to the genera *Debaryomyces*, *Meyerozyma*, *Torulaspora*, *Pichia*, *Clavispora*, *Cyberlindnera*, *Hanseniaspora*, *Geotrichum*, *Galactomyces*, and *Zygosaccharomyces* (Hallen-Adams & Suhr, 2017; Mar Rodríguez et al., 2015; Raimondi et al., 2019).

In gut diseases, most of the studies have focused on fungal community diversity and richness and characterization of fungal species, especially in inflammatory Bowel disease (IBD). Here we present a brief overview of Ascomycetes yeasts composition in several gut diseases, as described in previous reviews in a more comprehensive way (Chin et al., 2020; Chu et al., 2018; Gouba & Drancourt, 2015; Huseyin, O'Toole, et al., 2017; Iliev & Leonardi, 2017; Lai et al., 2019; Y. Li et al., 2019; Mahmoudi et al., 2021; Mukherjee et al., 2015; Richard & Sokol, 2019; Wu et al., 2021; X. Zhang et al., 2020). In general, differences within the fungal community were found when IBD patients were compared with healthy subjects. However, no substantial differences were found between Crohn's disease (CD) and ulcerative colitis (UC; L. Chen & Wang, 2022; Ott et al., 2008; Sokol et al., 2017). For the first time, in 1988, anti-*Saccharomyces cerevisiae* antibodies (ASCA) were found in the blood of CD patients, but not in UC patients (Main et al., 1988, p. 88). ASCA recognizes fungal cell wall peptidomannans (Sendid et al., 1998). However, subsequent studies showed that other yeasts of the genus *Candida*, such as *C. albicans* and *C. tropicalis*, displayed interactions with ASCA (Chehoud et al., 2015; Hoarau et al., 2016; Liguori et al., 2016; Sokol et al., 2017). Specifically, in IBD, increased abundances of *C. albicans*, *C. glabrata*, and *C. tropicalis* were observed, and the relative abundance of *C. albicans* was found to be differently correlated with the remission and relapse.

The relative abundance of *S. cerevisiae* is still a matter of debate. Sokol et al. (2017) found an enrichment of *Candida* spp. and a reduction of *S. cerevisiae* in Crohn's disease (CD) flare compared to remission. In our previous study (di Paola et al., 2020), we isolated *S. cerevisiae* and *Candida* spp. from fecal samples of pediatric IBD patients. *S. cerevisiae* was more abundant in CD patients compared to UC and healthy controls. Liguori et al. (2016) observed that *S. cerevisiae* was enriched in the noninflamed gut mucosa of CD patients. On the other hand, Chiaro et al. (2017) reported that *S. cerevisiae* is able to exacerbate DSS-induced colitis and affects gut barrier permeability by inducing overproduction of uric acid. In obese and overweight individuals, fungal gut dysbiosis was observed (Borges et al., 2018; Mar Rodríguez et al., 2015), as well as in irritable bowel syndrome (IBS) patients. In IBS, the principal changes were observed especially for the genera *Saccharomyces* and *Candida* (Botschuijver et al., 2017; Hong, Li, et al., 2020; Santelmann & Howard, 2005). The gut mycobiota in type II diabetes displayed different fungal composition at the phylum level, as well as at the genus level, compared to healthy individuals, with an increase of the genera *Candida* and *Meyerozima*, and a decrease of *Saccharomyces*, *Clavispora*, and *Wickerhamomyces* (Bhute et al., 2017; Jayasudha et al., 2020). An increased abundance of the genus *Candida* was reported in type I diabetic patients (Gosiewski et al., 2014; Soyucen et al., 2014). Gut microbial alterations are associated not only with gastrointestinal and metabolic disorders, but also with diseases affecting other distal organs. Differences in gut mycobiota composition have been investigated in various chronic conditions, ranging from GI to liver, skin, and cardiovascular diseases, especially colorectal cancer (Coker et al., 2019), alcoholic liver disease (Lang et al., 2020; Szabo, 2018; A.-M. Yang et al., 2017), chronic kidney disease (Hu et al., 2022), atopic dermatitis (Mok et al., 2021), and atherosclerosis (Chacón et al., 2018).

Moreover, mycobiota composition can influence the gut–brain axis (GBA) through immune and non-immune mediated crosstalk systems, as already reviewed by Enaud et al. (2018). GBA is defined as the multiple connections between gut microbiota and brain, and the ways they could influence the host (Cryan et al., 2019; Martin et al., 2018; Morais et al., 2021). Seminal research reveals dynamic interactions between gut microbes and their animal hosts that shape the composition and function of the neurological system (Clarke et al., 2013; Erny et al., 2015; Lyte, 2014; Sharon

et al., 2019). Despite being less studied than the bacterial counterpart, in the last years, some evidence has suggested the role of the mycobiome in communicating with the brain. For example, mycobiome dysbiosis has been found in patients with IBS (Botschuijver et al., 2017), a condition characterized by a microbiome–GBA disorder (Kennedy et al., 2014). Changes in the mycobiome have been observed in several neurological conditions and diseases, including anorexia (Gouba et al., 2014b), autism spectrum disorder (ASD; Strati et al., 2017), Rett syndrome (Strati, Cavalieri, et al., 2016), schizophrenia (Severance et al., 2012; Severance et al., 2016), anxiety disorders (Markey et al., 2020), multiple sclerosis (Gargano et al., 2022; Shah et al., 2021), and Parkinson's disease (reviewed in Neto & Sant'Ana, 2023). A recent study showed that probiotic *Saccharomyces boulardii* could participate in the regulation of microglia-induced neuroinflammation in Alzheimer's disease (AD) model mice, in particular through the regulation of the TLRs pathway to inhibit the neuroinflammation via the gut–brain axis (Ye et al., 2022). As well as for the bacterial part of the microbiota (El Aidy et al., 2014), it has been proposed that the mechanism behind the effects of mycobiota on the brain involves the immune system, through the modulation of cytokines production by intestinal fungi, resulting in the crossing of the blood–brain barrier (BBB) by these molecules via the bloodstream.

2.4 | Genitourinary tract

First studies on the fungal community in women's reproductive tract date back to 1929 (Carter et al., 1959, p. 195). The vaginal bacteriome is dominated by *Lactobacillus* species (Human Microbiome Project Consortium, 2012b; K. Li et al., 2012), and the low-pH environment caused by their lactic acid production inhibits the growth of most of the filamentous species, resulting in a selective fungal community (Underhill & Iliev, 2014). Nonetheless, using culture-dependent methods, researchers have investigated the vaginal fungal community in healthy volunteers and patients with diabetes (Nowakowska et al., 2004). Fungi were recovered by culture in 20%–60% of the samples. Without exception, the predominant member of the fungal community was *Candida albicans* (often >70%; Barousse et al., 2004; Goldacre et al., 1981; Holland et al., 2003; Nowakowska et al., 2004). Other epidemiological studies confirmed a greater abundance of *Candida*, especially *C. albicans*, making up 85%–95% of isolates (Landers et al., 2004; Sobel, 1986).

In the past 10 years, thanks to the advent of NGS technologies, several culture-independent studies showed that the vaginal mycobiota is mainly composed of yeasts belonging to *Ascomycota*, followed by Basydiomicota, for a total of 22 genera (Bradford & Ravel, 2017). The most ubiquitous natural colonizer is the genus *Candida* and, namely, the species *C. albicans*, followed by *C. glabrata*, and other *Candida* species including *C. krusei*, *C. tropicalis*, *C. parapsilosis*, *C. dubliniensis*, and *C. guillermondi* (Drell et al., 2013; Guo et al., 2012; Hu et al., 2022; Zheng et al., 2013). The load rate of *Candida* in healthy adults ranges from 30% to 70% (Huffnagle & Noverr, 2013). Other non-*Candida* Ascomycetes yeasts are *Saccharomyces cerevisiae* and *Pichia kudriavzevii* (Drell et al., 2013; Papaemmanouil et al., 2011). Several factors, such as antibiotic use, pregnancy, viral infection (HIV and HPV), and recurrent vulvovaginal candidiasis have been associated with alterations of the vaginal fungal community structure, commonly leading to *Candida* spp. colonization that could increase up to 40% during pregnancy due to estrogen levels and glycogen production (Farr et al., 2015; Guo et al., 2012). Regarding urine and the urinary tract, there are not enough studies yet to determine a proper urinary mycobiota. Before the advent of culture-independent analyses, the uninfected urinary tract had been assumed to be a sterile environment (Ackerman & Underhill, 2017). Nevertheless, some culture-dependent studies have shown the presence of *Candida* and *Saccharomyces* species both in healthy donors and patients (Hilt et al., 2014; Khasriya et al., 2013; Nickel et al., 2016; Pearce et al., 2014; Thomas-White et al., 2016). Moreover, a recent culture-independent characterization of 504 urine samples revealed the presence of 13 fungal species from 8 genera, including the Ascomycetes yeasts *Candida*, *Saccharomyces*, *Pichia*, and *Yarrowia* in 202 females (Nickel et al., 2020).

2.5 | Skin

Since the skin surface is the primary barrier between our body and the environment, it is exposed to an extremely high amount of different microorganisms. Nonetheless, it is populated by commensal species, both bacteria and fungi, which help to maintain homeostasis and mediate lipid and urea degradation (Boxberger et al., 2021; Ratanapokasatit et al., 2022; Zhu et al., 2020), as well as the development and activation of the host immune system (Jo et al., 2017). Deep sequencing approaches have demonstrated that skin harbors a unique bacterial and fungal microbiota (Costello et al., 2009; Findley et al., 2013; Grice et al., 2009; Grice & Segre, 2011; Tagami, 2008). The fungal community represents

around 10% of all the skin microbiota and consists of more than 150 genera (Findley et al., 2013; H. Li et al., 2018). Mycobiota of the skin is site-specific, and it depends mostly on the dry or sebaceous nature of the microenvironment (Grice et al., 2009; Leung et al., 2016). As the skin is a self-renewing organ, dead cells are continuously shed, providing an environment for saprophytic microbial growth. The most common fungi colonizing the human skin belongs to *Basidiomycota*, especially *Malassezia* species, which represent on average at least 57% of the total mycobiota of all skin areas (H. Li et al., 2018; Paulino et al., 2006; E. Zhang et al., 2011). Among ascomycetes yeasts, *Candida* is the most abundant genus, particularly *C. albicans*, *C. tropicalis*, *C. parapsilosis*, and *C. orthopsilosis*, followed by *S. cerevisiae* (Huffnagle & Noverr, 2013; Leong et al., 2019; Ward et al., 2018; Zhu et al., 2020). In the skin of infants, different abundances of *S. cerevisiae*, *C. tropicalis*, *C. parapsilosis*, *C. albicans*, and *C. orthopsilosis* were influenced by the delivery mode (Ward et al., 2018).

The skin microbiota study provides insights on the interactions between pathogenic and commensal fungal communities, and how these interactions can result in beneficial or pathologic outcomes. Fungal species often considered colonizers of healthy skin, in particular *Malassezia*, can become causal agents of diseases. Cutaneous inflammatory conditions, such as psoriasis, atopic dermatitis, pityriasis versicolor, folliculitis, seborrhoeic dermatitis, dandruff, and rosacea have been associated with dysbiosis of the cutaneous microbiota (Zeeuwen et al., 2013).

3 | MOST REPRESENTATIVES ASCOMYCETES YEASTS IN THE HUMAN MYCOBIOTA

As shown in the previous sections, several studies investigating the composition of human mycobiota, both in health and in disease, reached the consensus that the most representative genera in terms of abundance and distribution are Ascomycetes yeasts, in particular *Saccharomyces* and *Candida*. Here we provide an overview of these genera to introduce their relevant characteristics and relationships with the human host.

3.1 | *Saccharomyces* species

The genus *Saccharomyces* includes a wide population of wild and domesticated yeast species, these latter well-known to be related to human activities and to industrial applications, such as food and beverage fermentation (Sicard & Legras, 2011). Domestication has contributed to the genomic evolution of *Saccharomyces* species (Dujon & Louis, 2017; Gallone et al., 2016). The intensive research on population diversity and genome evolution of this genus (Dujon & Louis, 2017; Dunn & Sherlock, 2008; Hewitt et al., 2014; Liti et al., 2009; Morales & Dujon, 2012; Peris et al., 2018; Peter et al., 2018; Piatkowska et al., 2013; Schacherer et al., 2009; Shahait et al., 2022) and last taxonomic reannotation led to the identification of eight different species, namely *S. cerevisiae*, *S. paradoxus*, *S. mikatae*, *S. jurei*, *S. kudriavzevii*, *S. arboricola*, *S. eubayanus* and *S. uvarum*, and two natural hybrids, namely *S. bayanus*, and *S. pastorianus* (Alsammar & Delneri, 2020).

The last evidence indicated a large biodiversity of *Saccharomyces* species in the natural environment. Investigation of the natural ecological niches allowed us to discover wild environments, such as soil, bark, leaves, and insect guts, in which *Saccharomyces* species can inhabit (Libkind et al., 2011; Peter et al., 2018; Sampaio & Gonçalves, 2017; Stefanini et al., 2012, 2016). In the last decades, growing interest has been placed in the evolutionary process that drives genotypic and phenotypic diversity between yeast species populations to allow adaptation to different niches. Recently, the ecology of *S. cerevisiae* has also been extended to the study of the human gut (Di Paola et al., 2020; Nash et al., 2017; Ramazzotti et al., 2019). The prevalence of *S. cerevisiae* in the human GIT would not be surprising since it has been purposely ingested by humans worldwide for thousands of years through bread, beer, and other fermented foods and beverages (Cavalieri et al., 2003; McGovern et al., 2004), and its abundance is indeed related to the consumption of fermented products (Sun et al., 2021). It is also the most abundant species in early life (at 1–2 years of age), which is a crucial window of the infant dietary shift from breastmilk to solid food (Fiers et al., 2020; Schei et al., 2017).

The role of *Saccharomyces* spp. in health and disease has been investigated, but major issues remain (Goddard & Greig, 2015; Liguori et al., 2016; Liti, 2015; Sokol et al., 2017). In particular, (i) are there differences in terms of abundance of strains between health and disease conditions? (ii) are *Saccharomyces* strains from the human gut genotypically and phenotypically adapted to survive and colonize the gut environment or are they transient? and (iii) how related are strains with the gut environment and host immune system? In the gut environment, yeast survival is

difficult and fungi–bacteria and fungi–fungi competition for the same niche are high. It cannot be excluded that the presence of *Saccharomyces* in the gut is due to food ingestion. Our previous study (Di Paola et al., 2020) provided evidence of genetic and phenotypic differences between strains isolated from gut and non-gut environments (e.g., natural sources, fermentation). However, it could be assumed that a disease-specific gut environment may favor the expansion of yeast strains, through the onset of peculiar features that are likely to affect the yeast's fitness and interaction with the host, as observed in IBD conditions. In the same study (Di Paola et al., 2020), we observed that genetic and phenotypic differences (e.g., cell wall composition) among strains isolated from fecal samples of Crohn's disease patients reflected the strain-specific differences in eliciting host immune reactivity. It is possible to hypothesize that some *S. cerevisiae* strains may be a passenger, ingested with the diet and they could be capable of colonizing the host in certain conditions, such as the presence of a leaky gut or in case of a non-responsive host immune system.

3.2 | *Candida* species

The genus *Candida* comprises the highest number of different human-related species (Huffnagle & Noverr, 2013; Huseyin, O'Toole, et al., 2017; Oever & Netea, 2014; Romo & Kumamoto, 2020; Witherden et al., 2017), either pathogens or commensal, able to colonize the host since the birth (Hallen-Adams & Suhr, 2017, p. 201; Kondori et al., 2020; Mukherjee et al., 2014; Nash et al., 2017; Reef et al., 1998). As above reported, different species are commonly found on the skin, GIT, and genitourinary tract (Barousse et al., 2004; Fidel, 1998; Kühbacher et al., 2017; Neville et al., 2015; Odds, 1987). An extensive review of the survival strategies of *Candida* species within the human host has been published by Polke et al. (2015). *Candida* species can exhibit several virulence factors, such as adherence, biofilm formation, and secretion of hydrolytic enzymes that can increase their persistence within the host, as well as cause host cell damage (Silva et al., 2012). For these reasons, the scientific community has traditionally focused on disease-related studies (Kojic & Darouiche, 2004; Naglik et al., 2003; Odds, 1987, 1994; Spellberg et al., 2005; Thompson et al., 2010). Nevertheless, *Candida* spp. are also able to exert beneficial effects for the host, by shaping the development of mucosal immunity protecting from fungal infections (Atarashi et al., 2015; Ifrim et al., 2015; Markey et al., 2018). Out of approximately 200 known *Candida* species (Brandt, 2002; Yapar, 2014), at least 15 cause opportunistic infections in humans. Among these, *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* were found (Kapitan et al., 2019; Yapar, 2014). In the last 20 years, the number of infections identified as due to non-*C. Albicans Candida* (NCAC) species have increased significantly (Hani et al., 2015; Kauffman et al., 2000; Maubon et al., 2014; Ruan & Hsueh, 2009; Staniszewska, 2020). The apparent increased involvement of NCAC species in human candidiasis may partly be related to improvements in diagnostic methods (Liguori et al., 2009) or their inherently higher level of resistance to antifungals (González et al., 2008; Tortorano et al., 2021). While *C. tropicalis*, *C. parapsilosis*, and *C. krusei* can be found both as part of human mycobiota (Pfaller et al., 2011; Roilides et al., 2003; Trofa et al., 2008) and in different environmental niches (Carruba et al., 1991; Gadanho & Sampaio, 2005; Medeiros et al., 2008; Nielsen et al., 2005; Suh et al., 2008; Y.-L. Yang et al., 2012), *C. albicans* and *C. glabrata* are thought to be predominantly associated with host (Brandt, 2002; Gabaldón & Carreté, 2016), even if recent evidence suggests that latter seems to have environmental reservoirs (Gabaldón & Fairhead, 2019).

C. albicans represents by far the most studied yeast related to humans. It is an opportunistic pathogen that is vertically transmitted from the mother, and frequently inhabits the oral, vaginal, and GIT of healthy individuals as a harmless commensal (d'Enfert, 2009; Miranda et al., 2009; Mishra & Koh, 2018; Nash et al., 2017; Prieto et al., 2016; Zhai et al., 2020). Specific conditions, such as an unbalanced microbiota, a suppression immune system, and an impaired mucosal barrier can predispose to invasive infections (Kumamoto et al., 2020). Depending on the environment, *C. albicans* can switch reversibly between unicellular yeast (which can be additionally divided into white, gray opaque phenotypes), pseudohyphae, and true hyphae forms (Noble et al., 2017; Sudbery et al., 2004). Although both hyphal morphologies are necessary for virulence (Jacobsen et al., 2012), there is a consensus on the fact that yeast cells are best suited for dissemination and hyphal cells for tissue invasion (Gow et al., 2002; Jacobsen et al., 2012). Morphology transitions are related to different factors, ranging from physiological and chemical nature environment, to necessity mating or immune evasion (Miller & Johnson, 2002; Morschhäuser, 2010; Pande et al., 2013). These conditions are always correlated with huge changes in gene expression profiles (Mayer et al., 2013). In the absence of risk factors, infections and overgrowth of *C. albicans* are usually not severe. Oral, skin, and vaginal candidiasis are very common in human individuals (Kapitan et al., 2019). For example, around 75% of women experience at least one episode of vulvovaginal candidiasis during their reproductive age (Yano et al., 2019). Life-threatening systemic *C. albicans* infections can arise when

fungus enters the bloodstream, mostly from the host's GI tract (Gouba & Drancourt, 2015; Kumamoto, 2011; Miranda et al., 2009; Odds et al., 2006; Zhai et al., 2020), when immune defenses are compromised for different possible reasons (Koh et al., 2008; Papon et al., 2020). Through blood, the infection can disseminate among almost all organs (Pappas et al., 2018), the fungus is able to tune the type of infection thanks to its high genetic variability and adaptation (d'Enfert et al., 2021). Systemic infections can easily occur, mostly associated with predisposing conditions, immuno-depression, or following nosocomial infection (Dadar et al., 2018).

4 | FACTORS SHAPING THE MYCOBIOTA COMPOSITION

The scientific consensus on the high variability of the mycobiota in the human body, as observed both inter and intra-individuals across time, suggests a crucial impact of several factors in shaping the composition and diversity of the fungal communities (Figure 2). Colonization of the human body by fungi begins immediately after birth (Ward et al., 2018). Mother-to-child transfer (vertical transmission) is the initial source of fungi. The early mycobiota is influenced by the gestational age of a newborn, birth weight, delivery mode, and feeding. During human life, the mycobiota composition is influenced by the environment (horizontal transmission) and by a large number of endogenous and exogenous factors, including age, gender, diet, bacteriome, and medication (e.g., antibiotic and antifungal therapy). In the next sections, we will explore these factors.

4.1 | Host genetics

Similarly to the bacterial community, host genetics is able to shape the mycobiota composition and plays a key role in the severity and susceptibility to fungal infection (Duxbury et al., 2019; Maskarinec et al., 2016; Pana et al., 2014). Host–pathogen interaction can be strongly influenced by genetic variations arising in some key genes (Merkhofer & Klein, 2020). Gene polymorphisms are often associated with an increased incidence of opportunistic fungal diseases, and it is known that also epigenetic events are involved in disease progression (Dolinoy & Jirtle, 2008; Goodrich et al., 2017; Martin & Fry, 2018). Among the genetic factors that can lead to a host's susceptibility, mutations in the gene
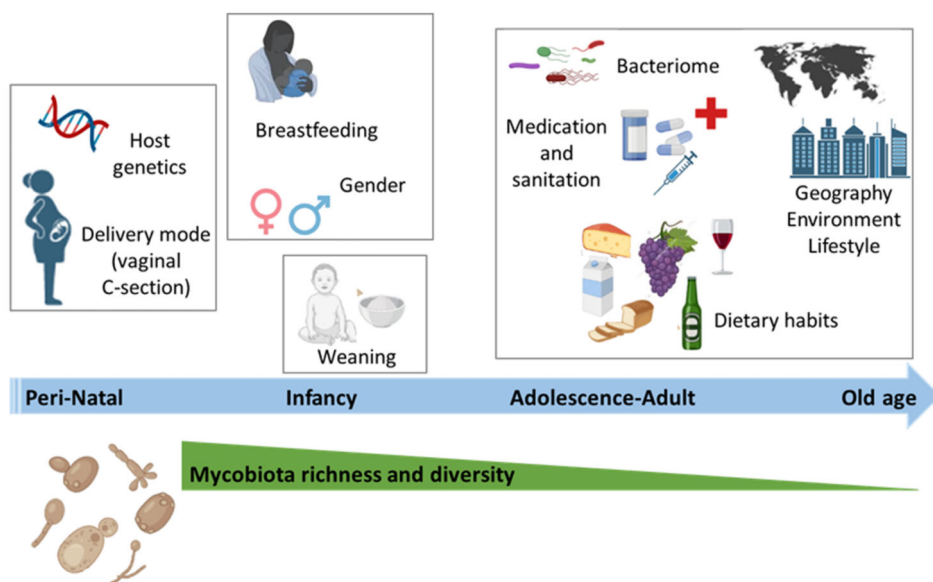

FIGURE 2 Factors affecting the human mycobiota across the lifespan. Primary fungal community colonization begins at birth, and the major factors contributing to the infant mycobiota composition are host genetics, gender, delivery mode, and feeding. The richness and diversity of mycobiota increase during infancy and gradually decrease from young adults to the elderly. During adulthood, other factors, including dietary habits, lifestyle, geography, medication, and sanitation contribute to influence the human mycobiota composition.

coding for host receptors (PRRs; e.g., TLR, CLR, NLR, RLR, MBL, dectins), single nucleotide polymorphisms (SNPs) in the gene coding for crucial mediators of immune response (TNF, INF, immunoglobulins, interleukins) and mutations in gene deputation to control inflammation, phagocytosis, and metabolism (e.g. ZNF341, STAT1/3, GATA2, NLRP3, PTX3, CARD9) represent elements of predisposition to fungal invasion. Indeed, immunodeficiency-causing mutations are strongly associated with impaired of mucosal immunity and overgrowth of fungal species, especially *Candida* genus, in multiple body sites (Lai et al., 2019, p. 201). Mutations affecting the T helper 17 cell responses (Patel & Kuchroo, 2015), or in genes involved in fungal sensing (e.g., dectin-3-Clec4d), as well as defects in mannose-binding lectin (MBL; Hammad et al., 2018) induce blooming of various *Candida* species (Bak-Romaniszyn et al., 2011; Nedovic et al., 2014). Hyphae of *C. albicans* are able to activate the inflammasome (Jaeger et al., 2016; Lev-Sagie et al., 2009), and polymorphisms in the NLRP3 inflammasome or mutations in CLEC7A (Dectin-1) or CARD9 are associated with susceptibility to vulvovaginitis. A comprehensive compilation of immune system genetic polymorphisms associated with susceptibility to fungal infections was reviewed by Naik et al. (2021).

Although the identification of monogenic susceptibility variants has made it possible to elucidate the pathways that are triggered in defense of both mucosal and systemic fungal infections, taken individually these variants are unable to explain the spectrum of susceptibility to mycosis that is recorded in the human populations. For this reason, recent studies have begun to investigate the relationships between genetic susceptibility to fungal infection and human ancestry (Domínguez-Andrés & Netea, 2019; Hughes et al., 2008). In spite of the fact that this research field is still in its infancy, the possibility of personalized therapeutic approaches against invasive fungal diseases is becoming increasingly concrete.

4.2 | Gender and age

Evidence of gender and age-related effects on mycobiota was reported for the first time in our study on healthy individuals, both children and adults (Strati, di Paola, et al., 2016). Females showed high fungal richness and biodiversity compared to males, with a higher prevalence of *Candida* species. Gender-dependent differences seem to be due to sex hormones, as observed in the mice model (Markle et al., 2013), or differences in dietary habits between females and males (Bolnick et al., 2014). Increased levels of *Candida* during ovulation, pregnancy, or following the use of oral contraception (hormonal therapies) could be associated with the window of opportunity to invade the host determined by a mild reduction of immune defenses (Farr et al., 2015; Guo et al., 2012; Lasarte et al., 2013; Salinas-Muñoz et al., 2018). The production of estradiol during the menstrual cycle has an anti-inflammatory effect, temporarily lowering the immune system during the phase of interaction between sperm and egg cells. The immune system lets its guard down when a woman is ovulating, increasing the likelihood of a sperm cell surviving in the reproductive tract. As a side effect, women who are ovulating, or on birth control pills, are more prone to yeast, bacterial and viral infections (Relloso et al., 2012). Unlike microbiota (Koenig et al., 2011; Lozupone et al., 2012; Yatsunenko et al., 2012), in humans the fungal community diversity decreases ranging from childhood to adult age (Chehoud et al., 2015; Jo et al., 2016; Strati, di Paola, et al., 2016).

The age-related changes in fungal communities appear to be more relevant in the first months of life (Schei et al., 2017; Wampach et al., 2017; Ward et al., 2017). Studies revealed that newborn infants between 1 and 4 months of age have a gut mycobiota dominated by the orders *Malasseziales* and *Saccharomycetales*, whereas *Saccharomycetales* (*Saccharomyces* and *Candida* genera) prevail in the range from older infants to adulthood (Fujimura et al., 2016). It has been hypothesized that a high percentage of the maternal mycobiota could be transferred to the newborn, consistently with pioneer works mainly based on *Candida* (Bliss et al., 2008; Waggoner-Fountain et al., 1996). Recent studies confirmed that newborn babies receive *C. albicans* strains from their mothers during vaginal delivery (Bliss et al., 2008; Schei et al., 2017). Conversely, cesarean-section-born children had a different stool mycobiota when compared vaginally delivered children (Wampach et al., 2017; Ward et al., 2017). Also, the initial colonization of the skin by fungi is shaped by the delivery mode (Ward et al., 2018). Compositional changes of the skin mycobiota were observed in several studies from childhood to adulthood (Grice & Segre, 2011; Jo et al., 2016), and similar patterns have been documented in other body sites (Ackerman & Underhill, 2017; Peters et al., 2017; Strati, di Paola, et al., 2016). *C. albicans* was significantly more abundant on the skin of infants who were born vaginally (Ward et al., 2018). Vaginal delivery is shown to promote oral yeast carriage (Azevedo et al., 2020), but the relative abundance of certain species, such as *Candida orthopsilosis*, is significantly higher in C-section-born infants (Ikebe et al., 2006; Ward et al., 2018). Interestingly, infant feeding (formula-fed or breast-fed) does not seem to affect the mycobiota composition (Azevedo et al., 2020; Darwazeh &

Al-Bashir, 1995; Oba et al., 2020), although human breast milk contains approximately 3.5×10^5 fungal cells per mL (Boix-Amorós et al., 2017).

Unlike childhood, mycobiota composition in older healthy individuals was less studied (Barrera-Vázquez & Gomez-Verjan, 2020, p. 201), although it was investigated in elderly diseased subjects (Alonso et al., 2018; Jayasudha et al., 2020; Nagpal et al., 2020).

Moreover, changes that naturally occur during aging could affect the fungal presence within the human microbial communities. For instance, age-related hyposalivation leads to a reduction of compounds with antimicrobial activity, increasing the occurrence of oral candidiasis (Dimopoulos et al., 2013). In Alzheimer's disease, it was observed that brain fungal infections showed a higher prevalence of fungi in elderly patients compared to younger ones, and that the most abundant genera were *Alternaria, Botrytis, Candida,* and *Malassezia* (Alonso et al., 2018). Overall, these findings show that a deeper characterization of the mycobiota could lead us to new insights for intervention strategies and therapeutic approaches aimed at promoting health and preventing the onset of disease, influencing a healthier aging process.

4.3 | Diet

Evidence demonstrated that diet is the most important factor that modulates bacterial community composition, especially in the gut (David et al., 2014; Graf et al., 2015; Shankar, 2021). The impact of diet in shaping the mycobiota has been studied since 1974 when Finegold et al. (1974) compared the culturable fungi from the stools of individuals who followed either Western or Japanese diets. Since then, diet-related studies have focused on the gut mycobiota. A lot of fungal species are introduced into our bodies through food and beverages and could potentially become more than transient colonizers (Belvoncikova et al., 2022; David et al., 2014; Hoffmann et al., 2013; Sun et al., 2021). Indeed, fungi and especially Ascomycetes yeasts are commonly associated with several food products, such as *Saccharomyces, Candida, Pichia, Galactomyces, Hanseniaspora, Debaryomyces, Brettanomyces, Zygosaccharomyces,* and *Wickerhamomyces* species. These fungi have been found in baking goods (Dangi et al., 2017; Y. Li et al., 2019), fruits (Tournas et al., 2006; Vadkertiová et al., 2012), fermented and acidophilus milk (Bell et al., 2018; Griffin et al., 2020; Reed & Nagodawithana, 1990), cheese (Bintsis, 2021), fermented beverages including wine, beer and sake (Jolly et al., 2014, p. 201; Venturini Copetti, 2019), and different meats and soy sauce (Venturini Copetti, 2019). The ingestion of these species through food has been shown to alter the gut mycobiota composition. For instance, *Candida* species were found to be positively associated with recent consumption of high amounts of carbohydrates and negatively with a diet high in proteins or fatty acids (Hoffmann et al., 2013), while *S. cerevisiae* was found reduced in the gut after a decreased intake of bread and beer (Auchtung et al., 2018). Moreover, the amount of the genus *Candida* in the gut was observed in association with a plant-based diet (David et al., 2014). In murine models, mice fed with a high-fat diet showed significant differences in gut mycobiota composition (Heisel et al., 2017). A recent study comparing fecal samples of Indian and Japanese individuals showed that polysaccharides in the Indian plant-rich diet led to an abundance of *Candida* in the gut (Pareek et al., 2019), providing additional evidence that diet is associated with changes to the mycobiota composition.

Related to diet, body weight was observed as a factor affecting the gut mycobiota composition. Evidence showed that gut fungal communities differ between overweight, obese, and lean subjects (Mar Rodríguez et al., 2015). Predominant Ascomycetes yeasts in overweight individuals were *Candida* and *Pichia,* whereas *Candida* and *Nakaseomyces* were found more abundant in obese individuals (Borges et al., 2018; Mar Rodríguez et al., 2015).

Overall, these findings offer the starting point to discuss whether some foodborne fungi found in the gut microbiota might be passenger species or transient colonizers, and whether the diet can serve as a source of diverse fungal species that can stably colonize the gut.

4.4 | Lifestyle, culture, and geography

Other factors affecting the composition of human microbial communities, that are closely related to diet are lifestyle, culture, and geography. In the last decades, several studies addressed the impact of these factors on gut bacterial communities. The main evidence showed that modern Western populations have reduced gut and skin microbiota diversity compared to that of traditional and rural populations (Angebault et al., 2013; Clemente et al., 2012; De Filippo

et al., 2010; Martínez et al., 2015; Yatsunenko et al., 2012). Regarding the mycobiota, there are limited findings of different mycobiota compositions according to different lifestyle, culture, and geography. For instance, in Wayampi Amerindian populations, in French Guiana, a relatively rich fungal diversity was observed, although a significantly lower prevalence of *C. albicans* was found compared to Western industrialized populations (Angebault et al., 2013). Moreover, in community-dwelling elderly Asian people—a low abundance of oral *Candida* species was found (Zakaria et al., 2017).

4.5 | Bacteriome

The coexistence and mutual influence of bacterial and fungal communities are well-known in all ecological systems. Bacterial communities' impact on mycobiota has been studied especially regarding *Candida* colonization in the human gut and genitourinary tract. Antibiotic treatments favor fungal overgrowth in both these sites (Fan et al., 2015; Spinillo et al., 1999; Xu, Schwartz, et al., 2008; Zaborin et al., 2014). Apart from dynamics competition between bacteria and fungi, several studies showed that bacteria affect fungal growth through production of fungistatic acids (Cottier et al., 2015; Mortensen & Clausen, 1996; Noverr et al., 2004), as well as reactive oxygen species (Fitzsimmons & Berry, 1994) and biosurfactants (Gibson et al., 2009; Hogan & Kolter, 2002; Velraeds et al., 1998) that inhibit the growth or the hyphal formation of *Candida* species. At the same time, other studies focus on the bacterial ability to produce metabolites that enhance the growth and pathogenesis of fungi (Adam et al., 2002; Gale & Sandoval, 1957; Neely et al., 1986; Xu, Lee, et al., 2008), showing synergistic interactions between these two kingdoms into the human bodies. Finally, also indirect activation of the host immune system against bacteria can lead to an impairment of *Candida* colonization (Lamas et al., 2016; Zelante et al., 2013). However, more studies are needed to deepen microbiota-related bacterial influences on other non-*Candida* species.

5 | METHODS TO CHARACTERIZE THE MYCOBIOTA AND TECHNOLOGICAL ISSUES

Historically, in vitro culturing was the primary method for fungal community investigation (Finegold et al., 1974), and still today, it is the only effective means for isolation, phenotypic, and biochemical characterization. In the past decade, our understanding of the prevalence and diversity of the fungal communities associated with ecological niches in human bodies has been expanded (Clemente et al., 2012; Erturk-Hasdemir & Kasper, 2013; Human Microbiome Project Consortium, 2012b; Tremaroli & Bäckhed, 2012), thanks to advances in NGS techniques and especially through amplicon-based approaches targeting the ribosomal DNA and the internal transcribed spacer (ITS) region, the primary genomic biomarker of fungi (Shaffer et al., 2022). However, a number of technical challenges have hampered the application of metagenomics to the study of the mycobiome, mainly (i) sample preparation, (ii) extraction of fungal genomic DNA, and (iii) paucity of properly annotated yeast and fungal reference genomes in public databases. Additionally, most of the methodologies used to explore the bacterial component of the microbiota are proving to be inadequate when used in the study of fungal communities. The absence of pipelines that are both specific and standardized for fungi, together with the lack of well-maintained databases, make mycobiota investigations still limited (Suhr & Hallen-Adams, 2015).

Despite their known diversities, fungi, similarly to bacteria, experience the same issues when it comes to talking in terms of culture-dependent approaches for their study (e.g., unknown or difficult-to-reproduce growth conditions in vitro, high time consumption, unsuitability for high-throughput analysis, the impossibility of unambiguous identification without molecular methods). However, to access the fungus itself, as well as its viability, metabolites production, phenotypic and functional characterization, and other host-adaptation aspects, culturomic techniques offer unquestionable and unparalleled advantages (Strati, di Paola, et al., 2016). Therefore, culture-dependent methods continue to be needful and of considerable interest for phenotypic and immunological characterization (Borges et al., 2018; Hamad et al., 2017).

Besides strain cultures, in vitro models of the human colon have been developed and refined to study the microorganisms associated with it (Auchtung et al., 2015; Barroso et al., 2015a, 2015b; McDonald et al., 2015; Takagi et al., 2016). Due to the complexity of both microbial communities and interactions, the implementation of in vitro models that enable the monitoring of changes induced by physiological or pathological variations in the host GIT is

increasingly allowing for more accurate mimicry of in vivo study conditions. However, none of the currently available models can simultaneously encompass all the key conditions found in the human colon, including the intricate microbiome–host interaction. The integration of microfluidics and bioengineering has been employed to replicate human intestinal functions in a small-scale fluid flow system, akin to a chip. Current models have evolved from static co-cultures (Bein et al., 2018) to co-cultures in continuous flow, resembling in vivo physiologic shear stress, and eventually, they have incorporated mechanical forces such as peristalsis (Kim et al., 2012). The initial focus of microfluidics-assisted investigations involving fungi centered on yeasts. Due to their single-cell nature, the transition from microfluidic studies on bacteria and mammalian cells was seamless, often starting by simply extending the application of established devices to yeasts (Wu et al., 2004).

The use of DNA as an identification marker in culture-independent techniques overcomes some of the problems, but it introduces others. Purification of genomic DNA is directly related to the efficiency with which different methods succeed in destroying the complex fungal cell wall, which is rich in glucans and chitin (Aimanianda et al., 2009; Gow et al., 2017; Valiante et al., 2015). This step turns out to be more complicated than for most bacteria, but it is well established that it requires, regardless of the starting matrix, the combination of mechanical (beads-mediated) and enzymatic lysis for efficient mycobiota analysis (Huseyin, Rubio, et al., 2017). Once total gDNA is obtained, it is possible to detect and identify fungi present within a complex sample by two culture-independent approaches both based on NGS technologies, namely metabarcoding and whole genome shotgun metagenomics. In metabarcoding, the choice of the barcode sequence and sequence-specific primers is crucial. Due to its characteristics, the rRNA gene locus represents the main fungal marker, just as it does for bacteria. In fungi, the rRNA gene locus consists of 3 ribosomal genes (18S rRNA, 5.8 rRNA, and 28S rRNA) separated by two spacer regions (ITS1 and ITS2; De Filippis et al., 2017; Nilsson et al., 2019). After being proposed by Schoch and colleagues as a possible universal fungal marker (Schoch et al., 2012), ITS has gained some fame in the last decade, although several drawbacks have emerged. For example, several findings have shown that neither of the two ITS regions can fully represent a synthetic fungal community, because of internal bias (Ali et al., 2019; Bellemain et al., 2010; Bokulich & Mills, 2013; Tedersoo & Lindahl, 2016). In fact, ITS1 is proven to be useful in identifying fungi belonging to the phylum *Basidiomycota*, while ITS2 the members belonging to the *Ascomycota* (Bellemain et al., 2010). However, after comparing primer sets specific to the rRNA 18S, ITS1, ITS2, and rRNA 26S genomic regions, Hoggard and colleagues proposed the use of the ITS2 region for the study of human mycobiota (Hoggard et al., 2018). This information was confirmed by the proposal of Nilsson and colleagues to target a subregion that could provide greater taxonomic resolution by the degenerate primer forward gITS7ngs and reverse ITS4ng (Nilsson et al., 2019).

Besides primer choice, the ITS has some intrinsic criticalities. First of all, the length variability (ranging from 200 to 800 bp), has a strong impact on PCR performance as well as on sequencing efficiency (De Filippis et al., 2017; Tang et al., 2015). The presence of intragenomic heterogeneity within a single species, may cause an overestimation of global fungal diversity, in addition to the ITS region being present in multiple copies within one species (Schoch et al., 2012). It is challenging to determine the fungal abundance accurately due to the large interspecific variation in ITS copies number, and care must be used when attempting to compare quantitatively different species found in mixed populations. Given the problems that have arisen with the ITS marker, several secondary markers have been proposed to complement the identification of fungal species (Huang et al., 2012; Morrison et al., 2020; Schoch et al., 2012; Stielow et al., 2015).

The choice of one or more reference genes is essential for standardization and promotion of large-scale investigations. However, in some instances, primer bias in targeted sequencing can be addressed by choosing the shotgun metagenomic technique.

Whole genome sequencing (WGS) is the most unbiased method due to its nonspecificity, but it is also one that is most susceptible to host DNA contamination, which can easily account for the majority of the sequenced reads in samples taken from soft tissues and biological fluids (Human Microbiome Project Consortium, 2012a). The study of the mycobiota is greatly impacted by this issue because fungi make up only a tiny percentage of all microorganisms and massive sequencing depth is demanded for downstream analysis. The low fungal abundance in human samples is currently limiting the wide-scale application of metagenomic WGS in human samples. This occurrence, which is not related to DNA extraction methods, highlights the low overall fungal abundance in vivo (Nash et al., 2017). Compared to metabarcoding, shotgun metagenomics is a much more expensive and computationally demanding approach, but it allows us to describe functional pathways and discover new functions (Morgan & Huttenhower, 2014). Among the most recent innovations, the introduction of long-read sequencing by Pacific Biosciences (PacBio) and Oxford Nanopore

technologies is bringing numerous advantages for WGS of organisms, including fungi, making it possible to resolve critical regions, such as highly repeated ones.

Regardless of the methodologies used to classify sequenced reads (assembly-based or assembly-free), probably the most concerning analytic challenge for mycobiota investigations is still the availability of cured fungal databases (Quince et al., 2017). Despite the fact that fungi are one of the largest branches of the Tree of Life, the number of high-quality fungal sequences in curated databases, such as SILVA database for rRNA sequences (Pruesse et al., 2007) or the UNITE database for ITS sequences (Abarenkov et al., 2010) is still significantly lower than that of available bacterial rRNA sequences. Over the past 10 years, several databases dedicated to fungal sequences have appeared. However, only a few of these are regularly maintained by a dedicated team of curators. This lack results in a substantial amount of unclassified reads, which might be addressed by producing additional high-quality metagenomic and whole-fungal genome assemblies (Mac Aogáin et al., 2019; Nash et al., 2017). Furthermore, confounding redundancies in fungal taxonomy and a lack of available fungal genomes make identification even more complex. For instance, sexual (telomorph) and asexual (anamorph) forms of the same fungus are frequently classified as separated taxa, with different approved names at the phylum level (Halwachs et al., 2017). Therefore, although a consensus on wet lab practices has not yet been reached, the lack of standardization of the pipelines employed for sequencing data analysis and the requirement to increase the number and the correct annotation of reference fungal genomes available in public databases are the aspects that most undermine this area of research. Data interpretation is in fact a challenging step in metagenomics and metabarcoding studies. Both methods currently allow for a more objective analysis of fungal phylogeny and precise identification, but they also produce increasing volumes of sequencing data that need to be properly stored and managed. Standardization of bioinformatic pipelines is still in its infancy, and a great effort is needed from the scientific community. Integration of all the previously mentioned aspects is fundamental to advancing the study of the mycobiome. A summary of the presented pros and cons of fungal identification approaches is shown in Figure 3.

6 | CONCLUSION

The genera *Saccharomyces* and *Candida*, belonging to the *Ascomycota* phylum, contain the larger number of species described to interact with the human host. The genus *Candida* is the most studied for its multiple types of relationship with the human host. In fact, several species of this genus, both commensals and pathogens, have been known to colonize different body sites since birth. The genus *Saccharomyces*, although forever considered a domesticated yeast, associated with food and beverage fermentations, has gained a role in investigations on human interaction in health and disease. The balance between pathogenic and commensal yeasts has been explored especially within the different districts of the human body. Over time, this has allowed the characterization and anatomical mapping of human fungal communities, also referred to as human mycobiota.

The composition of human mycobiota is affected by several factors throughout the human lifetime, mostly related to the environment and individual lifestyle. Due to the great variability among these factors, and to the crucial influence of the mycobiota in determining human health and disease status, it is essential to increase our knowledge and improve our technologies in order to overcome the challenges upon the fungal communities inhabiting the environmental ecosystem and our body.

Recent technological innovations in metagenomics are currently making it possible to improve mycobiota detection and deepen the mechanisms underlying host–fungi interaction. Culture-dependent approaches and the use of fungal laboratory strains allowed for the understanding of cellular and molecular mechanisms underlying the interaction with the host. However, the development of better culture-based approaches would be desirable to isolate fungal species of interest to assign appropriate taxonomy and relevant phenotypic characteristics in order to enhance mycobiome research.

As far as culture-independent methods, the relatively recent advancements in metagenomics allowed descriptive studies and comparative analyses of the mycobiome in different ecosystems. However, different methodologies can give different accounts of the diversity present in any given sample. Further advances in this research area will be needed for the development of well-curated and referenced databases for mycobiome studies. Furthermore, increasing the number of reference fungal genomes available in public databases, and the development of bioinformatic and computational tools specific for mycobiome need to be implemented, to overcome the existing challenges in studying the mycobiota.
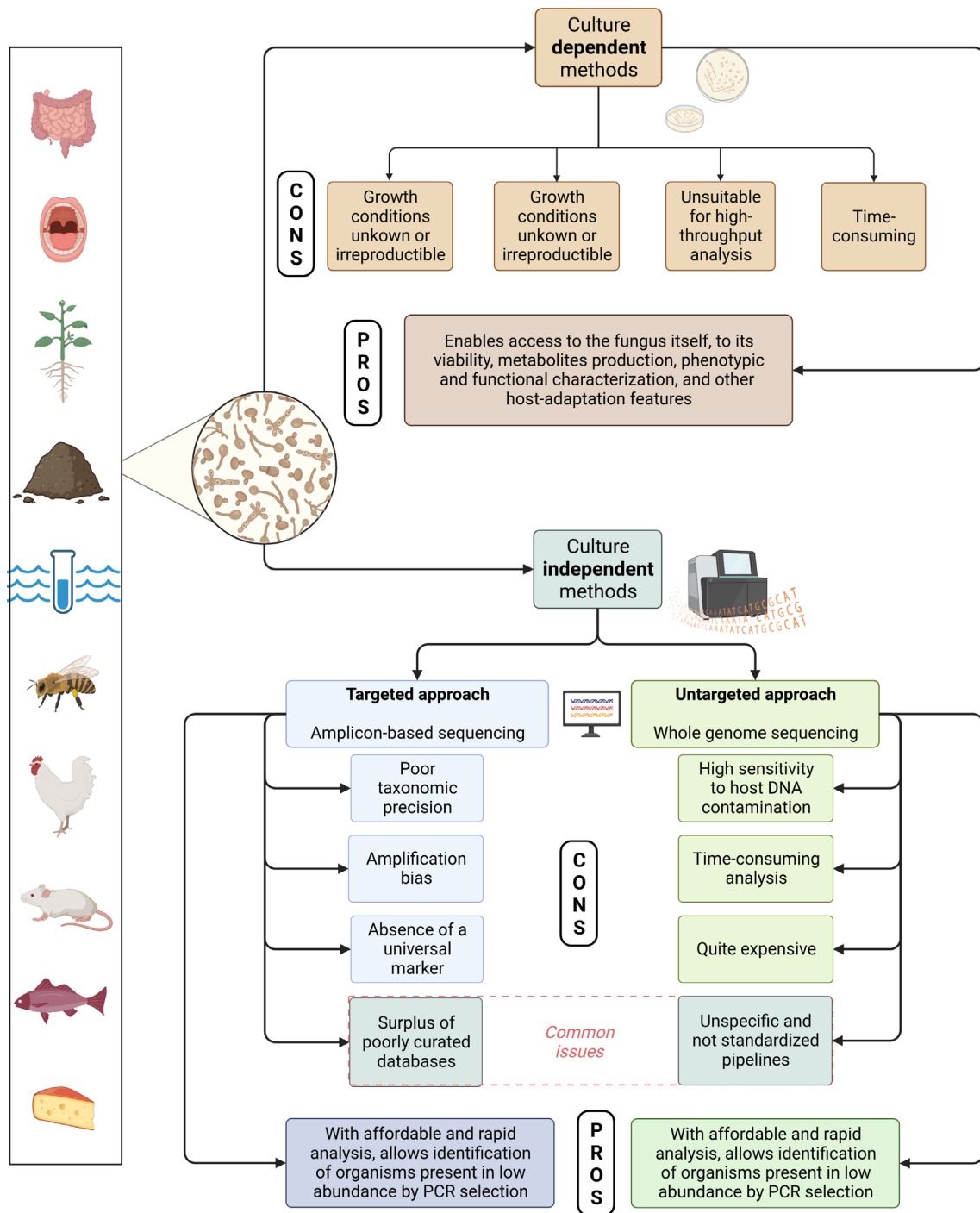
FIGURE 3 Schematic representation of culture-dependent and independent approaches for fungal community identification from different biologic matrices. Based on Renzi et al. (2024).

The dawn of the postgenomic era has ushered in an era of data-driven precision biology, and the mycobiota is no exception. The integration of omics technologies offers a panoramic view of the molecular tapestry woven within the fungal communities residing in the human host. Looking forward, the future holds exciting prospects for leveraging this integrative approach to unravel the functional intricacies that define the mycobiota's response to environmental cues and individual lifestyles. The ability to move beyond descriptive taxonomic studies and venture into the realm of functional metagenomics is poised to revolutionize our understanding of mycobiota dynamics. Predictive modeling based on these functional insights could pave the way for personalized interventions tailored to an individual's unique mycobiota profile, offering unprecedented opportunities for precision medicine.

In conclusion, the future of mycobiota research is undeniably intertwined with the evolution of integrative omics analysis.

AUTHOR CONTRIBUTIONS
Stefano Nenciarini: Conceptualization (equal); writing – original draft (lead); writing – review and editing (equal). **Sonia Renzi:** Conceptualization (equal); writing – original draft (lead); writing – review and editing (equal). **Monica Di Paola:** Writing – original draft (supporting); writing – review and editing (lead). **Niccolò Meriggi:** Writing – original draft (supporting); writing – review and editing (equal). **DUCCIO CAVALIERI:** Conceptualization (equal); supervision (lead); writing – review and editing (equal).

CONFLICT OF INTEREST STATEMENT
All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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