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Nasira, 2025
ISSN: 2579-0781

International Digital Organization for Scientific Research
IDOSR JOURNAL OF EXPERIMENTAL SCIENCES 11(3): 152-163, 2025.
https://doi.org/10.59298/IDOSR/JES/113.152163
IDOSRJES11300000

Narrative Review of the Mycobiome in Health and Disease

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ABSTRACT

The human mycobiome, representing the fungal fraction of the microbiome, has emerged as a key regulator of health and disease despite its relatively small abundance. Fungal communities inhabit diverse niches including the gastrointestinal tract, respiratory system, skin, and mucosal surfaces, where they engage in complex interactions with bacteria, host immunity, and environmental factors. Increasing evidence links mycobiome dysbiosis with inflammatory, autoimmune, metabolic, respiratory, and neuropsychiatric disorders. Pathogenic fungi such as *Candida albicans* can exacerbate inflammation and immune dysfunction, while commensal fungi including *Saccharomyces* contribute to immune tolerance and homeostasis. The mycobiome also participates in inter-kingdom signaling with bacteria, influences host metabolism, and modulates neuroimmune pathways relevant to mental health. Advances in sequencing technologies and bioinformatics have refined our ability to characterize fungal communities, but significant gaps remain in understanding mechanistic roles. Therapeutic approaches such as fungal probiotics, dietary interventions, antifungal modulation, and fecal microbiota transplantation demonstrate the translational potential of mycobiome research. This review synthesizes current evidence on the diversity, function, and clinical implications of the mycobiome, highlighting its underappreciated role as a determinant of human health.

Keywords: Mycobiome, Fungal dysbiosis, Host–microbe interactions, Autoimmune and metabolic disorders and fungal therapeutics

INTRODUCTION

The mycobiome, defined as the fungal component of the human microbiome, is an integral constituent of the human host. It has been linked to both human health and disease, thereby indicating a more systemic influence than previously recognized. Consequently, the mycobiome deserves greater emphasis in literature and a heightened focus from researchers and practitioners working across health, mental health, and disease [1]. The mammalian mycobiome is a diverse and dynamic ecological system in inherent relationship with the human host. The human body nurtures numerous complex and varied niches that accommodate the transient presence and/or residence of symbiotic, commensal, and pathogenic fungi. Human tissues and surfaces in contact with the external environment provide habitats for the mycobiome; for example, fungal communities inhabit mucosal surfaces such as the gastrointestinal and respiratory tracts [1], as well as integumentary sites including the scalp, nails, and hair. The structural and functional composition of these populations exhibits considerable temporal and geographical variation throughout the human life cycle. Established at birth, the mycobiome constitutes a foundational biological milieu for the human host, underpinning the ability of hosts to respond and adapt to both internal and external biotic or abiotic challenges [1].

The Role of the Mycobiome in Human Health

Fungi represent a minute yet influential proportion of the human microbiome. Diversity and composition vary according to life stage, diet, and environmental exposure, localizing predominantly within the respiratory and gastrointestinal tracts [2, 1]. Mycobiome constituents have co-evolved with host immune systems and the gut microbiome to mediate immune function, inflammation, and homeostasis; the section “Interactions with the Gut Microbiome” describes these relationships in greater detail [2].

Mycobiome Diversity and Composition

The human mycobiome displays low diversity with large inter-individual variation. The dominant phyla are Ascomycota and Basidiomycota, with the ratio of these phyla differing considerably between individuals. Common genera include Candida, Saccharomyces, Penicillium, and Aspergillus, some of which may constitute the core mycobiota [3]. Fungi frequently enter the human gut via diet or the environment and do not necessarily establish stable colonization. Most fungal–bacterial interactions comprise positive correlations, many of which probably originate from environmental fungi [3].

Impact on Immune Function

The mycobiome regulates immune homeostasis and influences immune development, thereby modulating protection against pathogens and immune tolerance [2]. Considerable variation occurs between body sites, and differences exist between health and disease. Immunophenotyping of the fungal strains in Crohn’s disease revealed a bias of the immune response towards an inflammatory state, confirmed by the capacity of competitive Candida albicans to exacerbate colitis in a mouse model [4]. Furthermore, the depletion of the fungal or bacterial microbiota from antibiotic treatment influences both pathology and the immune response towards Candida species in this model. Lactic acid bacteria and Saccharomyces boulardii protect the host from Candida-driven gastrointestinal pathologies and reduce the expression of inflammatory mediators. Fungal dysbiosis can be an initiator of intestinal inflammation, and the intestinal fungal community influences immune responses and disease progression through opportunistic fungi [4]. In contrast to Candida, non-pathogenic species such as Saccharomyces are protective and maintain immune homeostasis. The mycobiota can induce immunomodulatory effects through diverse mechanisms in several diseases, including gastrointestinal disorders, multiple sclerosis, and airway allergy. Some commensal fungi are able to mediate immune regulation, though others aggravate inflammation and promote disease pathogenesis.

Interactions with the Gut Microbiome

An up-to-date understanding of the gut microbiota requires considering the interactions between fungal and bacterial communities, which are complex and influenced by local spatial organization and environmental conditions such as temperature and pH [5]. Host immune responses further modulate these interactions. Clinical observations of fungal complications in antibiotic-treated patients support the concept that balanced fungal and bacterial communities are essential for maintaining a healthy microbiome; this balance is a therapeutic target in managing associated diseases. Fungi influence microbial-community assembly and succession dynamics worldwide in natural and host-associated environments, and like bacteria they engage in antagonistic, mutualistic, and commensal relationships. At the microbial scale, the effect of a fungus on bacterial growth depends strongly on the species involved, microspatial structure, and environmental conditions [5]. For example, on a limited nutrient source, a fungus sometimes facilitates bacterial growth by redistributing nutrients and sometimes inhibits bacterial growth via various mechanisms [5]. Nevertheless, the broader consequences for community structure, diversity, and function remain largely unexplored and consequently no longer serve as a guiding framework for investigating host-microbial relationships. Developing this synthetic and predictive understanding with respect to host health and disease is critical since: (i) both fungi and bacteria have emerged as important agents in various diseases; (ii) microbiome research, with its focus on holistic community properties, has revolutionized approaches to health and disease over the past decade; and (iii) many fundamental features of the interaction patterns are unknown [5].

Mycobiome in Disease States

Fungal infections represent an ancient challenge for the immune system. Indirect evidence, such as the expansion of fungi in dysbiotic states, or the expansion of fungal-specific Th17 cells during diseases associated with mycobiome dysbiosis or, for example, the increased susceptibility of CARD9-deficient individuals to fungal infections indicates that the mycobiome is implicated in the regulation of immune homeostasis [6]. Pathogenic fungi are frequently associated with systemic infections, even in developed countries where access to healthcare is widely available. While localized mycosis is usually mild and treatable, systemic infections remain a challenge, being frequently associated with immunocompromised states. The most common forms of systemic mycosis are cryptococcosis, candidiasis, aspergillosis, and pneumocystis, each associated with a particular fungal species [1]. Autoimmune disorders such as rheumatoid arthritis and Bechet’s disease have an undoubted connection with the mycobiome, although the mechanistic explanations remain elusive. Several studies have observed a reduction of fungal diversity in multiple sclerosis and, conversely, in ankylosing spondylitis the ratio of fungal to bacterial populations is dramatically increased. An expansion of Candida albicans in the gut has been observed in autistic patients; however, the limited number of studies available at this point makes it difficult to elucidate the biological role of this colonization [1, 6].

Fungal Infections and Pathogenesis

The mycobiome constitutes the community of fungi residing in and on the human body. Fungal species play an important role in human health, influencing the character of immune responses, although the function of many mycobiome elements remains poorly understood [7]. Fungi inhabit various niches, including the skin and the respiratory and gastrointestinal (GI) tracts. The GI tract harbours six genera of fungi spanning 37 species, with Candida, Saccharomyces, and Cladosporium accounting for 70% to 80% of the fungi 8. Fungal communities are highly variable, although species such as Candida albicans and Saccharomyces cerevisiae are frequently identified [9]. The mycobiome interacts closely with the bacterial microbiome and with host immune systems through pathogen recognition receptors such as dectin-1 and mannose receptors. Such interactions inform antibody production and the body's immune responses to other challenges. Extensive fungal–bacterial–host interactions occur at mucosal surfaces throughout the body. An imbalance in any constituent has potentially broad and systemic consequences [7, 9].

Mycobiome Alterations in Chronic Diseases

Alterations in the mycobiota have been linked to the development of numerous chronic diseases. In a study investigating fecal samples from individuals with chronic hepatitis B virus (HBV) infection, researchers identified fewer fungal species and lower fungal diversity. Notably, increased abundances of Candida and Aspergillus were observed in HBV patients. Similarly, a pilot study examining the serum mycobiome in ankylosing spondylitis (AS) patients revealed significant differences in fungal genera compared to healthy controls [2]. In the context of microbial vaginosis, a condition characterized by reduced Lactobacillus and elevated anaerobic bacteria, aberrant fungal populations have been described. Although autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome have been linked to mycobiome alterations, detailed compositional analyses remain limited [2].

Association with Autoimmune Disorders

Autoimmune disorders remain understudied from the perspective of the human microbiome; however, the mycobiome may play a significant role in their development. Over recent decades, a dramatic increase in autoimmune and inflammatory diseases has been observed in developed regions, exceeding what can be attributed to genetic factors alone [10]. While autoimmunity was historically considered primarily as the immune system attacking a sterile self, contemporary research increasingly links autoimmune reactions to microbial influences and dysbiosis. Advanced microbiome analyses have implicated microbial communities in diseases such as rheumatoid arthritis, type 1 diabetes, psoriasis, systemic lupus erythematosus, Crohn's disease, and multiple sclerosis [10]. The microbiome can affect the immune system through various mechanisms, including Toll-like receptor stimulation, molecular mimicry, epitope spreading, and epigenetic modifications that impact gene function [11]. The human microbiome significantly influences mucosal immunity and may contribute to the development of systemic autoimmunity, particularly in genetically susceptible individuals. Recent methodological advances have clarified the general nature of microbial changes associated with autoimmune diseases, but the high variability of the microbiome over short periods complicates interpretations of causality [11]. Molecular mimicry offers one hypothesis by which microbes might trigger autoimmune reactions, yet current evidence favors a model where the microbiota exacerbates immune disorders in predisposed hosts [11]. Increasingly, research is shifting from cataloging associations to elucidating the immunologic and metabolic roles of the microbiome with the aim of developing therapies such as fecal microbiota transplantation and bioactive molecules derived from microbial metabolism. Mouse models provide valuable simplicity for mechanistic studies, but substantial differences between human and murine microbiota, along with the influences of environment and genetics, necessitate careful consideration in extrapolating results [11]. The timing of microbiota-targeted interventions appears critical; for example, early probiotic supplementation in infancy has been associated with decreased risk of autoimmune disorders. Although most investigations have concentrated on the intestinal microbiota, other communities, including those found on the skin and at mucosal sites, as well as viral and fungal components, also merit attention for their roles in autoimmunity [11].

Mycobiome and Metabolic Disorders

The human mycobiome exerts substantial influence on the environmental microbiome, developing in early life and implicated in numerous diseases [6]. Several mycobiome characteristics appear as risk factors and represent potential therapeutic targets for metabolic diseases, reflecting distinct host–microbial crosstalk compared with non-transformed tissues [2, 12]. However, the specific contribution of the mycobiome remains to be established for most conditions [10]. The abundance of a limited number of genera correlates with obesity-related traits, while compositional alterations of the mycobiome observed in metabolic syndrome and diabetes share certain characteristics and seem to depend on the mycobiome composition of the unaffected state [10].

Obesity and Metabolic Syndrome

A connection between the mycobiome and obesity, metabolic syndrome, and diabetes has been suggested. Obesity has become a worldwide epidemic affecting approximately 39% of adults in 2016, and this is projected to increase [13]. The gut microbiota has been implicated in the development of obesity in humans and mouse models [14]. The human gut microbiome and body metabolism have significant implications for these diseases [14]. A gut microbiome with increased capacity for energy harvest is associated with obesity. Gut microbiome richness correlates to metabolic markers, yet these relationships and their relevance to health remain elusive. Artificial sweeteners can induce glucose intolerance by altering the gut microbiota [14]. These findings provide additional evidence for the involvement of the gut microbiome in host immune interactions and metabolic regulation, which appear to be pivotal in understanding obesity and metabolic syndrome. Recent data firmly establish the gut microbiome as a key environmental factor contributing to metabolic health [14].

Diabetes and the Mycobiome

Alterations to the gut mycobiome are associated with obesity and metabolic syndrome [15] and depression. Diabetes is closely linked to obesity and metabolic syndrome and is associated with mycobiome dysbiosis [16]. Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia due to insulin resistance or deficiency and accounts for most diabetes cases. Changes to the intestinal mycobiome of people with T2DM may also contribute to the prevalence of secondary eye diseases [15]. The gut mycobiomes of healthy people and those with T2DM and diabetic retinopathy (DR) were shown to differ. Dysbiosis associated with T2DM may play a role in the development of DR, and new therapies could be developed to treat these conditions by targeting fungal species. Notably, mycobiome dysbiosis persists despite therapeutic efforts to directly address blood glucose regulation [16]. A characteristic pattern of fungal dysbiosis may provide diagnostic information on the initiation and progression of T2DM and associated diseases and serve as a biomarker in larger populations. Mycobiome dysbiosis is also associated with Crohn's disease and ulcerative colitis, which are considered predisposing factors for the development of colitis-associated colorectal cancer. The fungal phylum Zygomycota, as well as the Mucor genus and Rhizopus species, are depleted in Crohn's disease and colitis-associated colorectal cancer [15, 16].

The Mycobiome in Respiratory Diseases

Asthma and allergic diseases represent a heterogeneous spectrum of conditions characterized by immunological dysregulation in response to genetic and environmental factors [17]. Fungal-related respiratory allergy is especially important as circulatory immunoglobulin E (IgE) directed against fungi and the occurrence of such allergy has progressively increased in incidence. Aspergillus species is commonly associated with allergic hypersensitivity, yet species such as Penicillium, Cladosporium, Alternaria, and Candida are also contributory. The relationship between the human microbiome and respiratory disease is an expanding area of research. Microbial colonization during the neonatal period has been shown to influence the T-helper type 1 (Th1)/Th2 balance and the subsequent development of asthma and other allergy-related diseases [17]. Chronic obstructive pulmonary disease (COPD) is among the most common respiratory diseases worldwide, characterized by persistent respiratory symptoms associated with airflow limitation and sustained airway inflammation. Despite limitations on the extent to which antifungal agents can be used due to cost or drug–drug interactions, techniques that develop the understanding of Aspergillus sensitization and colonization of the airway could have an important role in directing and informing clinical practice. A better understanding of how Aspergillus species influence COPD pathogenesis could potentially be used to develop fungal-targeted therapeutics [17]. The airway mycobiome of patients with COPD and bronchiectasis is characterized by Aspergillus, Penicillium, and Clavispora, and the associated presence of distinct Aspergillus fumigatus and Aspergillus terreus species. A clinically relevant Aspergillus-associated signature encompassing mycobiome compositional, inflammatory, and host-response features has been identified, and such profiles are strongly associated with increased exacerbations and mortality in bronchiectasis [17].

Asthma and Allergies

Asthma is characterized by airway inflammation, hyper-responsiveness, and mucus hypersecretion, resulting in airflow obstruction. Asthmatic inflammation is heterogeneous and can be broadly classified into type 2 and non-type-2 inflammatory patterns. The gut–lung axis suggests that alterations in the intestinal microbiota can modulate immune function within the lungs despite the absence of microorganism translocation [18]. Recent studies underscore the critical role of the gut–lung axis in the pathogenesis of asthma. Investigations into intestinal dysbiosis in asthma have predominantly focused on bacteria and the capacity of bacterial metabolites, such as short-chain fatty acids, to regulate airway inflammation [18]. However, the healthy gut also harbors a wide array of commensal fungi; genera including Aspergillus and Penicillium are well-known asthma triggers upon inhalation. Sequencing approaches targeting the internal transcribed spacer (ITS) region or the 18S rRNA gene are commonly employed to characterize the gastrointestinal fungal community. This section reviews the role of the gut fungal microbiome in asthma, the mechanistic links between the gut mycobiome and asthma, strategies to therapeutically manipulate the mycobiome in asthma, and emerging directions for future research [18].

Chronic Obstructive Pulmonary Disease (COPD)

Microorganisms are frequently detected in the airways of patients with stable chronic obstructive pulmonary disease (COPD) or during acute exacerbations. An initial insult by noxious or infectious stimuli, followed by impaired innate immune defenses and subsequent microbial colonization, leads to epithelial injury and inflammation, which perpetuates cycles of chronic infection and airway damage in COPD. Whereas bacterial and viral infections are well established in COPD, the role of fungi remains undefined despite their high abundance in the environment [17]. COPD is characterized by persistent respiratory symptoms and airflow limitation caused by distal airway abnormalities, primarily due to exposure to noxious particles or gases. Chronic airway inflammation results in small airway changes and lung tissue destruction. The prevalence is expected to increase further, with approximately 5 million annual deaths [19]. The airway microbiome is implicated in COPD progression, with dysbiosis associated with poorer outcomes. Immune activation driven by airway microbiota contributes to disease progression. Dysbiosis may mediate airway inflammation through interactions between airway bacteria and the immune system, involving metabolic and epigenetic changes that modulate immune responses [19].

Mycobiome and Mental Health

The involvement of the mycobiome in neuroimmune interactions provides a promising framework to further explore how fungi influence mental health. Although mycobiome–brain axis interactions remain largely unexplored, fungal dysbiosis is consistently linked with digestive disorders such as irritable bowel syndrome (IBS) [5]. IBS symptoms are characterized by altered cognitive function, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and gut bacterial dysbiosis, each of which is associated with depression and anxiety. In a rat model, fungal dysbiosis correlates with visceral hypersensitivity, and therapeutic intervention via probiotic supplementation improves gastrointestinal symptoms. Furthermore, individuals with inflammatory bowel disease (IBD) exhibit a modest increase in fungal load alongside disease-specific inter-kingdom changes involving Saccharomyces, Candida, Malassezia, Cladosporium, and Cyberlindnera [5]. Psychiatric comorbidities in IBD, including anxiety and depression, are linked to elevated systemic inflammation, HPA axis dysregulation, and elevated circulating microbial components such as lipopolysaccharide. Fungal activity modulates cytokine production in co-culture with immune cells, yet its role in systemic inflammation and neuroimmune crosstalk remains to be determined. Collectively, these findings suggest that physical, behavioural, and biological traits observed in severe fungal infections are also present in individuals with chronic fungal dysbiosis and mental illness [5].

Fungal Influence on Neuroinflammation

CNS disorders, including multiple sclerosis, Alzheimer's and Parkinson's diseases, and amyotrophic lateral sclerosis, have been associated with fungal communities [5]. Fungi impact the gut–brain axis (GBA) directly through neuro-immuno-endocrine mechanisms and indirectly via bacterial interactions [20]. The gut mycobiome modulates systemic inflammation and influences the immune response [21]. Evidence for a fungal contribution to neuroinflammation is found in irritable bowel syndrome (IBS), where dysbiosis of the mycobiome correlates with visceral hypersensitivity in animal and human models. The pro-inflammatory role of the mycobiome is further demonstrated by the attenuation of neurological damage following treatment with probiotic Saccharomyces strains, which restore fungal composition and reduce visceral hypersensitivity in a stress-induced animal model of IBS. Shifts in mycobiome composition, particularly increased fungal burden and disease-specific inter-kingdom alterations are reported in inflammatory bowel disease (IBD), a condition that features psychiatric comorbidities such as depression and anxiety [20, 21]. These comorbidities are linked to elevated systemic inflammation, cytokine modulations, and perturbations of the hypothalamic, pituitary, and adrenal axis, implicating fungi in both the immune and neuroinflammatory responses [20, 21].

Mycobiome in Depression and Anxiety

The mycobiome, synonymous with fungal colonies, is an integral yet often neglected component of human-commensal microbial communities spanning the gastrointestinal, respiratory, urogenital, and dermal systems [5]. Despite constituting less than 0.1% of the total gut microbiome, fungi play an essential part in influencing normal functions of the brain, lung, gastrointestinal tract, and immune system, thereby offering potential applications for clinical medicine. Fungal mycobiota impact neuro-immuno-endocrine mediators that act upon gut–brain physiology, modulating neuroinflammatory pathways and suggesting that mycobiome dysbiosis may contribute to the genesis and exacerbation of mental disorders such as depression and anxiety [5, 20, 21].

Environmental Factors Influencing the Mycobiome

Numerous environmental factors influence the composition and diversity of the mycobiome indirectly through interactions with the host immune system or by affecting co-existing microbial communities. Dietary patterns exert a marked influence on both bacterial and fungal richness. A vegetarian diet reduces mycobiome diversity while a diet rich in carbohydrates improves it [2]. The metabolism of carbohydrates by fungi can produce toxins that damage the host and exacerbate a range of gut disorders. Excess carbohydrate consumption also alters the expression of Candida genes encoding enzymes involved in the degradation of host gut proteins, a process that precedes invasion [2]. The widely prescribed antibiotic drug ciprofloxacin increases fungal load by disrupting the natural bacterial gut environment of humans and typically increases Candida albicans colonization. Antifungals may also disturb the delicate balance between the fungal and bacterial microbiomes by inhibiting non-pathogenic fungi and allowing bacterial community expansion with potentially negative consequences. Additional gut microbiome constituents modulated through the diet include Faecalibacterium and Dorea, which show opposite abundance shifts during dietary change. Faecalibacterium prausnitzii possesses anti-inflammatory properties and Dorea's role in pathogenesis remains unclear [2]. Although alcohol can impact bacterial richness, it is generally not associated with alterations of the mycobiome at the genus level. Further investigation across multiple cohorts will be necessary to better determine the effects of environmental factors on the mycobiome in human health and disease.

Dietary Influences

Diet which includes food and nutrition, feeding behaviours, and dietary patterns is a crucial factor shaping the human mycobiome, although it has not yet been comprehensively characterised. Specific fungal genera correlate with dietary habits of polar explorers and Chinese and Italian cohorts that include both normal and unhealthy subjects; Saccharomyces tends to associate with plant-rich diets (pasta, vegetables, and fruit), Penicillium with diets rich in meat and fish, Candida with diets rich in carbohydrates, and Malassezia with diets rich in fat [2]. Semi-quantitative analysis reveals that among abundant species, the amount of C. albicans significantly varies across healthy and unhealthy subjects within the Chinese cohort. Vegetables seem to negatively influence Mucor and Candida growth (the latter by up to 70%), whereas food rich in carbohydrates especially favours Saccharomyces-vulnerability groups. Other fungal species, such as C. albicans, C. parapsilosis, and A. ruber, exhibit clusters of positive covariances, indicating higher frequency of co-presence. C. albicans, particularly, negatively covaries with several species (e.g., A. ruber, C. dubliniensis, and L. aphanocladii), suggesting mutual exclusion or competition; subjects harbouring C. albicans are more often affected or at higher risk of gastrointestinal dysfunctions or infections [2]. An ethnogeographically defined cohort investigated with multi-omics reveals that the gut mycobiome strongly associates with long-term dietary habits [22]. Dairy consumption contributes most to the variation in the fungal community, showing a positive association with Saccharomyces and an inverse association with Candida. Considering that bacterial α-diversity correlates positively with Saccharomyces and negatively with Candida, dairy consumption might partly sustain gut health by modulating the mycobiome and bacteriome relationship [2].

AAntibiotics and Other Medications

The administration of antibiotics, particularly in early life, has discernible effects on fungal microbiota. Antibiotic use may increase the presence of Candida as a consequence of the medication's impact on indigenous bacterial communities [23]. Alternatively, antibiotic administration can promote fungal colonization via immunomodulatory properties. Relapse rates of mucosal candidiasis following antibiotic therapy are often elevated, signifying that antibiotics have complex interactions with fungi beyond the eradication of bacterial competitors [24]. Antibiotics directed against anaerobic bacteria indirectly modify fungal growth by diminishing protective commensal Clostridia species, thereby triggering a dysregulated inflammatory response dependent on the transcription factor HIF-1α. Antibiotic therapy also influences fungal pathogenic functions when bacteria are present, suggesting indirect effects on fungal gene expression during antibiotic treatments [25]. Other medications have associations with mycobiome alterations. Proton pump inhibitors enable Candida to expand owing to increased gastric pH and decreased acidity. Chemotherapeutic agents generally produce a reduction of native flora and subsequent dysbiotic states [23, 24, 25].

Lifestyle Factors

Lifestyle is increasingly recognized as a critical modulator of the mycobiome. Diet has a significant impact on the composition of the gut mycobiota, and may be an important lever to regulate or target the fungal microbiome for health purposes. Gut mycobiota profiles display ethno-geographical and age-specific characteristics, with shifts related to consumption of fungal-rich foods or food groups, including cheese or dairy [22]. Because beta-diversity analysis is reported as the most sensitive method for dietary tracking of the mycobiome, the impact of everyday meals can be accurately assessed to quantify responses to different diets or identify components that influence mycobiome composition. Habitual diet and long-term food consumption operate to shape the gut mycobiota, as shown by the extent of temporal profiling available. Dietary components are a major determinant of fungal assembly and metabolic activity in the gastrointestinal tract [2]. A diet rich in saturated fats is associated with augmented Ascomycota and Basidiomycota genera in adult humans, while a high-fat mouse diet results in weight gain and a decrease in fungal diversity, generalized reduction in the abundance of Saccharomyces, and pyramiding of the mycobiota toward several genera of the Basidiomycota. Mold-contaminated foods are linked to an abundance of Penicillium and Aspergillus, while a diet rich in mushrooms is linked to a dominant representation of the Pleosporales [2]. Prior antibiotic intake results in amplified mycobiome responses to dietary stimuli. Diets enriched with fiber or fat regulate the diversity and composition of the gut microbiota in healthy individuals. Dietary supplementation with carbohydrates or proteins impinges on fungal proliferation [2]. A range of antibiotics and xenobiotic substances are key modulators of the mycobiome and induce modifications with consequent pathological developments that include diarrhea and Clostridioides difficile infection.

Methodologies for Mycobiome Research

As techniques for examining microbial communities improve, a detailed understanding of the mycobiome is emerging in healthy individuals and in those at risk for or affected by disease. In this context, the gut mycobiome the fungal community residing in the gastrointestinal tract has garnered increased attention for its potential influence on host function and human health [1]. Platforms and tools for mycobiome studies encompass three key analytic stages the collection of specimens, sequencing of fungal nucleic acids, and computational pipelines for quality-filtering sequencing data, clustering sequences into phylotypes, and deriving mycobiome profiles [26]. Such sequence-based profiling workflows enable nucleotide- and taxonomically accurate characterizations of the human mycobiome, including relative abundances of prominent fungal genera associated with health and disease.

Sampling Techniques

Research on the human mycobiome is emerging with technological advancements, and an important factor in designing any mycobiome study is the choice of mycobiome sampling technique [26]. The ideal mycobiome sampling method depends on the host niche under investigation and the research question to be addressed. Once samples are collected, DNA is extracted, the ITS (Internal Transcribed Spacer) region of the rRNA gene cluster or a representative subregion is amplified, and amplicons are sequenced to identify fungi present and characterize the community [2].

Sequencing Technologies

Advances in next-generation sequencing technologies have considerably improved the resolution of fungal community profiling and, by extension, our ability to define the human mycobiome [27]. Despite these advances, it remains challenging to assess fungal diversity and record the mycobiome in human and environmental niches accurately. High-throughput and cost-efficient technologies have contributed to the development of well-established culture-independent tools to perform DNA sequencing of entire mycobiome communities and offer a highly effective alternative to traditional protocols for mycobiome analysis [27]. Two sequencing approaches, metagenomic and amplicon, are available to target the mycobiome; the metagenomic approach retrieves the complete genomic content of fungal species, while amplicon sequencing involves the selective amplification of fungal-specific conserved regions such as the 18S ribosomal RNA (rRNA), the 28S rRNA, or the internal transcribed spacer (ITS) regions [27]. The amplicon-based technology offers a detailed snapshot of the fungal microbiome composition, especially the ITS sequencing, which has proven to be a powerful tool for resolving fungal communities at the species level. Algorithms and software for high-throughput amplicon sequencing can reliably assign ITS sequences at various taxonomic levels, from kingdom to genus, species, and subspecies [27].

Bioinformatics Approaches

Bioinformatics approaches encompass the profiling and analysis of microbial communities using amplicon or metagenomic sequencing in conjunction with computational pipelines. Fungal metagenomics has established molecular guidelines for investigation to improve understanding of inter-kingdom interactions and host responses [1]. The human microbiome plays a fundamental role in health and disease. Global961mers and the increase of metagenomic sequencing data enabled the establishment of a healthy human reference gene catalogue, which identifies common or unique microbial community features at the gene level. Microbial co-occurrence and co-exclusion relationships have been used to identify potential microbes influencing host physiology and environmental changes [26]. Bacteria are conventionally considered the major community members contributing to the host's biological traits. However, fungi are fundamental components of the microbial world in all environments [28]. Bioinformatics approaches are commonly employed to explore the composition of bacterial and fungal communities in the gut, skin, and lungs, and to characterize the nature of their interactions [1]. Investigations of the human mycobiome reported large differences in fungal diversity and richness in patients suffering from chronic diseases. By assessing these differences, bioinformatics facilitates an improved understanding of the biological role of fungi within the human ecosystem and the pathogenesis of related diseases [26].

Therapeutic Implications of the Mycobiome

Mycobiome-targeted therapies are emerging with ongoing research aiming to modulate gut fungal communities for health improvement. Although the roles of bacteria-centered probiotic formulations in maintaining gastrointestinal barrier function and modulating the immune system have long been recognized, the existence of probiotics based on fungal strains was revealed only in the last decades [2]. Saccharomyces boulardii is the most commonly used fungal probiotic and appears to have multiple mechanisms of action such as the induction of secretory IgA, boosting of secretory and luminal immunoglobulins, and the expression of low-molecular-weight molecules that strengthen tight junction function and thus lower gut permeability [2]. The administration of S. boulardii has also been shown to counteract the dysbiotic effects of antibiotics on the gut microbiome and thus is widely used in combination with antibiotic regimens. In addition, mycobiome modulation seems promising in several other disorders. For example, fecal microbiome transplantation (FMT)-based gut fungal clearance has been successful in inducing remission of recurrent Clostridium difficile infections and in acute graft-versus-host disease (GVHD)-related diarrhea [6]. On the contrary, the gut fungal community appears to remain unchanged in patients with multiple sclerosis (MS) who undergo FMT, suggesting different mechanistic modes on health and disease need [1]. Nevertheless, the identification of altered fungal profiles confirms the mycobiome as an essential player in the control of the NLRP3 inflammasome and may help define a broader therapeutic role with considerable potential [1].

Probiotics and Fungal Therapies

Probiotics consist of living microorganisms that, when administered in adequate amounts, provide a health benefit to the host [7]. Certain lactobacilli and bifidobacteria strains are the most widely used probiotic bacteria. With the increasing understanding of the complex interactions within the gut and other sites, fungal probiotics have also been considered to influence host health. S. boulardii probiotic is most commonly used for and studied in the prevention and curing of diarrhea. These probiotics also play a significant role in the treatment of several gastrointestinal diseases, e.g., Clostridium difficile infection (CDI), inflammatory bowel disease, and irritable bowel syndrome, either alone or combined with probiotic bacteria [7]. In addition to the mycobiome's contribution to humans throughout life, fungal species have been widely used for medicinal and therapeutic purposes. Fungal metabolites are prevalent pharmaceuticals, of which the best-known example is penicillin, an antibiotic from Penicillium. Other drug examples include cholesterol-lowering lovastatin compounds synthesized by Aspergillus and Monascus and the immunosuppressant cyclosporine produced by Tolypocladium. Immunosuppression with drugs such as cyclosporine is vital in transplantation medicine to reduce graft rejection [7]. The fruiting bodies of fungi have been used for centuries for their health benefits, e.g., Ganoderma spp. to improve cancer and other disease treatment, Polyporus umbellatus as a diuretic agent, and many other beneficial activities [7].

Mycobiome Modulation Strategies

Alterations in the mycobiome have aroused tremendous interest in several medical fields. The abundance and composition of the fungal community in the human gut correlate with a myriad of health and disease conditions, sometimes opening the way to therapeutic solutions. The clinical contexts potentially benefiting from mycobiome modulation include autoimmune diseases, cancer, infections, obesity, chronic hepatitis, inflammatory bowel disease, mental illness-associated inflammation, and neurodegenerative diseases, among others [2]. However, the mycobiome remains to be harnessed from a clinical perspective, since a single isolate can be either beneficial or detrimental depending on the strain, hence the quest for an exhaustive compendium of each commensal with indication of which of the many isolates are desirable. The Saccharomyces cerevisiae species is a good example: as a dominant ever-present species in the human gut and one of the primary yeast groups in the environmental/food chain, it represents an interesting therapeutic tool, yet its clinical role is far from fully understood. Extensive studies on the bacteria/fungi gut axis may accelerate the translation of clinical solutions into therapies [6].

Future Directions in Mycobiome Research

The characterization of the human mycobiome is a scientific topic in development. The research methods considered in the previous section can furthermore be extended to overcome current limitations and improve its characterization, and have been recently described [29]. Technology will also continue providing new additional opportunities. The mycobiome is increasingly studied jointly with the bacterial microbiome and constitutes, therefore, another promising instance of multi-trophic interactions. Approaches combining synchronous real-time measurements of fungal, bacterial, and archaeal ATP using bioluminescence together with fluorescent in situ hybridization (FISH) are one example under development that appears to provide relevant information [7]. Joining analytical and modelling efforts is also expected to improve the characterization of such a dynamic system [6]. Finally, artificial intelligence and deep learning techniques applied to available data are currently considered and could be the framework supporting a new generation of studies in the near future.

Emerging Technologies

Numerous technologies enable detailed investigation of the mycobiome. Shotgun metagenomics uses primers for all genomic DNA within samples, allowing unbiased analysis of all microbial components. Metatranscriptomics sequences RNA molecules, identifying active genes of the mycobiome, although RNA's short lifespan and potential for post-sampling changes present challenges. Proteomics characterizes the mycobiome by detecting expressed proteins and conducting targeted analyses to identify expressed fungal enzymes. Metabolomics analyses small molecules, including those produced by fungi, permitting direct study of mycobiome activity and interactions, but taxonomic assignment remains difficult without comprehensive reference data [1]. Fungal morphology greatly affects detection and identification. Molds generate numerous spores, increasing detectability. Filamentous hyphae, long, branching structures, are often fragile and can be destroyed during sample processing, reducing recovery efficiency. Yeasts, either singularly or in small clusters, have a sturdier structure or tend to survive extraction procedures better [29]. These differences in persistence and abundance must be accounted for during analysis and interpretation [29].

Interdisciplinary Approaches

The mycobiome constitutes a fundamental element of human anatomy and physiology [6]. Interactions between fungi, host, and microbiota play crucial roles in host physiology in health and disease. In recent years, new protocols, techniques, and approaches, including culture, sequencing, bioinformatics, and databases, have been developed for consistently profiling the mycobiota. Studies of mycobiome malfunction have paved the way for promising strategies and therapeutic alternatives that may facilitate the re-establishment of a healthy mycobiome [26]. Interdisciplinary approaches with molecular, cellular, and ecological perspectives constitute a fertile field in mycobiome research.

Challenges in Mycobiome Studies

There are interconnected challenges in mycobiome studies. Conclusions regarding a "core mycobiome" remain elusive as gastrointestinal fungi often reflect ingested airborne spores and foodborne species [7]. While next-generation sequencing uncovers considerable diversity, many detected fungi are allochthonous and less relevant to resident communities. Hence, targeted standard approaches sensitive enough to capture low-biomass organisms may offer greater utility. Effective experimental design should account for substantial individual variability along with geographic and dietary influences [26]. Chemotherapy-driven dysbiosis and the mycobiome's role in other immunocompromised states, such as hematologic malignancies and HIV infection, highlight the need to characterize fungal colonization, host responses, and emerging diagnostics. Precise clinical correlations rely on accurate sample processing; therefore, recommended protocols include swabs, lavage, expectoration, or biopsy specimens combined with optimized DNA extraction techniques to ensure reproducibility. Fungal involvement in chronic conditions like atopic dermatitis and autoimmune disorders further underscores the importance of defining community configurations in both tumorigenic and immunological contexts [26].

Standardization of Methods

The human mycobiome plays a significant role in immunological imprinting and in the pathogenesis of chronic inflammatory and autoimmune diseases [26]. Studies of the mycobiome, however, are hindered by a lack of standardized techniques. Few standardized methods exist for sampling, DNA extraction, and analysis of fungal communities, making it difficult to compare the results of different studies or to extrapolate meaningful conclusions. Studies based on targeted amplicon sequencing have relied almost exclusively on ITS1 or ITS2 primers, but published mycobiome analyses typically employ primers from one or multiple analogue target regions for small subunit (SSU, 18S rRNA), large subunit (LSU, 28S rRNA), or internal transcribed spacer (ITS1, ITS2) regions [30]. Sequences from the 18S region are relatively conserved, making fungal discrimination difficult, while 28S and ITS regions provide better resolution between species. The absence of rigorous protocols for method validation, therefore, necessitates the integration and comparison of distinct methodological choices to determine their effects on results [26, 30].

Ethical Considerations

Biobanking of human biological samples is an essential step to allow a microbiome-wide association study on large cohorts. Biobank samples should be collected, stored, and transferred under strict conditions to prevent changes in the initial taxonomic profile. Samples can be contaminated by technical handling (e.g., barcode mislabelling, cross-contamination, and reagent contamination), whereas the DNA may be degraded by improper freezing, thawing, and storage for long periods [31]. Microbiome research presents several ethical questions regarding ownership, benefit sharing, and research implications [32]. Microbiome research participants may be exposed to novel and unanticipated forms of discrimination, which can arise at many levels of categorization, and include socio-economic factors, cultural or ethnic background. Marginalized sectors of society who already suffer from discrimination, such as minorities and those with obesity, may find that microbiome research leads to a greater “scientific” basis for marginalization. Association of diseases such as cancer with a microbial aetiology (whether correct or incorrect) may lead to stigmatization of groups reminiscent of those associated with certain infectious diseases [31, 32].

CONCLUSION

The mycobiome represents a dynamic and essential component of the human microbiome with broad implications for health and disease. While traditionally overshadowed by bacterial communities, fungi are now recognized as influential players in immune regulation, metabolism, infection, and even neuropsychiatric conditions. Dysbiosis of fungal populations can exacerbate chronic inflammation, predispose to infection, and disrupt host–microbe balance. Yet, the mycobiome also provides opportunities for therapeutic innovation, from fungal probiotics like *Saccharomyces boulardii* to targeted dietary and microbiome-modulating strategies. Continued advances in sequencing, computational analysis, and inter-kingdom interaction research will be pivotal to fully elucidating fungal contributions to human biology. Integrating mycobiome studies into mainstream microbiome research is essential to develop holistic interventions for complex diseases and to expand our understanding of host–microbe ecology.

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CITE AS: Nasira A. Sitar (2025). Narrative Review of the Mycobiome in Health and Disease. IDOSR JOURNAL OF EXPERIMENTAL SCIENCES 11(3): 152-163. https://doi.org/10.59298/IDOSR/JES/113.152163