Voyage Journal of Scientific Research and Exploration (VJSRE) *Vol . 1 Issue 1*
ISSN (Online): 3007-3898, ISSN (Print): 3007-388X, March 2024

UNVEILING THE FUNGAL FRONTIER: EXPLORING THE ROLE OF FUNGI IN THE GUT MICROBIOME AND HUMAN HEALTH.

Waseem Ahmed Khattak[1*], Minhas Elahi[1], Asif Kamal[1], Momal Batool[1], Fazli Maula[1]&Atika Noor[1]

[1]Plant Mycology Research Laboratory, Department of Plant Sciences, Faculty of Biological Sciences, Quaid-I-Azam University, Islamabad 45320, Pakistan

Correspondence: waseemkhattack@bs.qau.edu.pk

Abstract

This literature review discusses recent research's that have emphasized the relevance of fungi in the gut microbiome and their influence on human health. Fungi were long thought to be minor actors in the gut microbiome, but they now interact with other members of the cytoplasm and the host's immune system, influencing physiological processes such as digestion, metabolism, and the immune system. The literature review examines the principal fungus species present in the human gut, the interaction of fungi and bacteria, the activities of fungi in the gut microbiome, their influence on human health, fungal-based therapeutics for gut diseases, disease susceptibility, and the gut mycobiome. While fungal communities help the gut microbiota, several studies reveal that fungal population imbalances can contribute to problems of health such as inflammatory disorders, bowel disease, obesity, and diabetes type 2. Literature review also emphasizes the important relationship between bacteria and fungus, as well as how antibiotic treatment targeting bacteria might mistakenly result in fungal dysbiosis. While there is accumulating evidence of considerable interaction between bacteria and fungus in the mammalian gastrointestinal tract, the study indicates that additional research is needed to completely understand the molecular pathways underlying these in vivo interactions.

Keywords: Fungi, Gut Microbiome, Human Health, Interaction, Bacteria

Introduction

The complex ecology of the human gut microbiome is home to millions of organisms, including bacteria, viruses, archaea and fungi. According to recent research, fungi once believed to be a tiny component of the gut microbiome are now recognised as being essential to preserving human health. They can influence several physiological processes, such as metabolism, immunological response, and gastrointestinal function, through interactions with other cytoplasmic organisms and the immune system of the host. The most recent information about fungi's role in the microbiota of the gut and their impact on human health is highlighted in this article (Ghannoum *et al*., 2010).

Numerous factors have been demonstrated to influence fungal colonisation of the gut, such as host genetics, antibiotic use, and diet. Healthy individuals have small amounts of fungi in their bodies, which are thought to be beneficial to the gut flora. However, alterations in the balance between fungal and bacterial development or excess of genera have been connected to several illnesses, including as type 2 diabetes, obesity, and inflammatory bowel disease (Iliev *et al.,* 2012). Recent research has also revealed that fungus in the gut microbiome can interact with the host's immune system to alter the immune system's activity. Fungi have been discovered to affect immune response by a variety of processes including antigen presentation, cytokine generation after generation, and immune cell activation. The development of autoimmune diseases and allergens has been attributed to symbiosis of the gut microbiome, including modifications in fungus populations (Sokol e*t al*., 2012). This review describes the gut microbiome fungi and their impact on the human health. Figures shows the main features summarized in this review article. Our main objectives are: (1) Major fungal species in human gut; (2) Interaction between fungi & bacteria; (3) Functions of fungi in gut microbiome; (4) Gut microbiome fungi impact on human health; (5) Fungal-based therapies for gut disorders; (6) disease susceptibility and gut mycobiome.

Materials & Methods

This research review basedon published and technical sources related with notable fungal species found in the human gut microbiome, their impact on human health, disease susceptibility and gut mycobiome and therapies for gut disorder.

Results

Numerous attempts have been carried out worldwide some are summarized below. Fiers *et al.,* (2019) discovered the commonly recognised authentic gut symbiotic fungus. *Candida albicans* is the most common fungus found in routinely disposed of human waste. Therefore, it is thought that the mould is a typical component of the microbiota seen in the human gut (Odds, 1987 & Spellberg *et al.,* 2012). *C. albicans* does not appear to have a significant environmental reservoir, indicating that it has undergone substantial co-evolution with both its host and cohabiting microbes (Table 1). In otherwise healthy individuals, the fungus is a common cause of fastidious mucosal illness, and it may establish colonies in a variety of body areas, such as the mouth, skin, and vagina (Revankar and Sobel, 2011). Furthermore, *Candida albicans*could enter the circulation from the human stomach, where it may infect almost all vital organs and can cause death (Koh *et al.,* 2008 & Zhao *et al.,* 2020). According to Clancy and Nguyen (2012), individuals with compromised immune systems, such as cancer patients undergoing chemotherapy or recipients of organ transplants, are at a higher risk of developing widespread *Candida* infections. In Europe, invasive candidiasis causes 1.09 instances for every 1,000 hospital admissions and around 10 cases per 100,000 individuals, according to (Yapar, 2014).

Table 1. Fungal species of significance are frequently detected in the human gut.

Species Names	Observations
Candida albicans	fungus that is most seen in the digestive tracts of adults. leading Th17 cell inducers.
Candida glabrata	Pathogen having opportunistic nature. In the gastrointestinal tract, with an undetermined role.
Candida parapsilosis	The gastrointestinal functions of an opportunistic pathogen are unclear.
Saccharomyces spp	Although these kinds of yeast regularly show up in stool tests (because to their inclusion in a variety of drinks and dietary needs), they are not thought to be natural residents of the gut of an individual.
Rhodotorulamucilaginosa	Increased abundance in newborns is linked to childhood atopy (Fujimura *et al*., 2016).
Malassezia restricta	This skin fungus may not be a symbiont of the human stomach, even though it frequently appears in stool testing (Fierse*t al.*, 2019).
Issatchenkiaorientalis(*Candida krusei*)	Atopic wheeze relates to greater abundance in babies (Arrieta *et al*., 2018).

Interactions within the gut microbiome, dynamic relationship between gut fungi and bacteria.

Hundreds, if not thousands, of additional microbial species cohabit alongside *C. albicans* in the digestive tract. Therefore, it is quite likely that the gut microbiota might have a significant influence on the growth of fungi. In fact, antibiotic therapy in humans was found to cause *Candida* overgrowth in the 1960s Seelig, (1966 a, b), probably because of the suppression of rival bacteria. Antibiotic medication considerably alters the fungal makeup, according to recent research employing technology to monitor the whole gut fungal population (Sovran *et al.,* 2018). As a result, unknowingly causing fungal dysbiosis when targeting bacteria. Additionally, there is evidence that altering fungus can affect bacterial communities. In one such study, mice treated with antifungal medications showed significant changes in the makeup of their bacterial population (Wheeler *et al.,* 2016). It was discovered in another study using gnotobiotic mice that a small number of fungi five species might be responsible for significant ecological alterations in the gut microbial makeup (Bernardes *et al*., 2020). The same study showed that inter kingdom interactions (bacteria-fungi) have a particularly strong impact on the early-life assembly of bacterial and fungal communities. Though the evidence of major interactions between bacteria and fungi in the mammalian digestive system is mounting, little progress has been made in understanding the molecular mechanisms underlying these interactions in vivo. That's not to say that studies haven't been conducted on how various bacteria affect the abilities of specific fungus, like *Candida albicans*, or vice versa. The overwhelming majority of information on the interactions between fungus and bacteria, however, comes from in vitro systems (such bio film development) or non-intestinal mucosal environments (like oral or vaginal). Since several of these studies have already been briefly summarised in a recent publication, they won't be discussed in additional detail here (Richard and Sokol, 2019). It's probable that studies examining interactions in the real intestinal process are sparse because of the great diversity of the mammalian gut microbiota and the lack of a practical and appropriate animal model of gut fungal colonisation.

According to two studies that examined the basis of antagonistic interactions between bacteria and *Candida albicans* in mice used as models of intestinal colonisation, *Candida albicans* is involved in the host's immune response and has been shown to protect against fatal *Clostridium difficile* infections (Markey *et al.,* 2018). The impact seems to be mediated, at least partially, by the fungus increasing the production of the pro-inflammatory cytokine IL-17. Many Bacteroidetes and clostridial Firmicutes were shown to inhibit Candida albicans in the mouse intestine in the other investigation (Fan *et al.,* 2015). These bacteria enhanced the development of gut mucosal immune defences unique to *Candida albicans*, hence suppressing fungal growth. Commensal bacteria often use priming responses by the host's immune system as a defence mechanism against pathogens that invade the mammalian host (Khosravi and Mazmanian, 2013). Although these processes are frequently mentioned regarding antagonistic bacterium-bacteria relationships, the two examples provided here demonstrate that the idea may also be applied to relationships between fungus and bacteria. It is important to note that, based on the two studies discussed here, *Candida albicans* functions as both a fungal pathogen that the host is protected from by immune system responses triggered by commensal bacteria and a commensal that can elicit a response to protect the host from a bacterial pathogen.

Table 2. Exploring interaction types and their relationships.

Type	Description
Mutualism, Competition	Mutualistic interactions were discovered between some fungal species and bacteria in the gut microbiota, in which fungus aided nutrient intake by bacteria while competing for resources in other situations.
Antagonism, Commensalism	Investigated the antagonistic relationships between bacterial and fungal strains, where some fungus produced compounds that inhibited the development of the bacteria. There have also been reports of commensal partnerships, in which some bacteria profit from the fungal degradation of complicated substrates without causing harm to the fungus.
Syntrophy, Amensalism	Investigated syntrophic relationships, which are beneficial partnerships between fungus and bacteria that occur when they work together to metabolise complicated substrates. On the other hand, amensalistic associations have been reported, in which fungus impeded bacterial development by either secreting toxins or competing with them for scarce resources.
Predation, Parasitism	Examined fungal predation on bacterial species, which resulted in a drop in bacterial abundance. Furthermore, interactions between parasites were noted, wherein certain fungus colonise bacterial biofilms and compromise their activity, hence influencing gut homeostasis.
Mutualism, Neutralism	Discovered mutualistic interactions in the gut microbiota between bacteria and fungus that profited from each other's metabolic assistance. Additionally, neutral interactions between bacteria and fungus were reported, in which their coexistence had no discernible impact on one another's growth or functionality.

Functions of fungi in gut microbiome

Fungi are an essential component of the gut microbiome, serving a variety of functions which enhance host health. We address recent discoveries of the functions of fungus in the gut microbiome along with references to relevant papers.

Digestion and metabolism: Complex carbohydrate metabolism and digestion can be aided by the presence of fungi in the gut flora. For instance, in the rumen of cows, the fungus *Orpinomyces* sp. may ferment lingo cellulosic materials (Liggenstoffer *et al.,* 2014). Human dietary fibers have been shown to be broken down by the fungus *Saccharomyces cerevisiae*, resulting in the production of fatty acids with a short chain that the host may use as an energy source (Morrison & Preston, 2016). Autoimmune metabolism the immune system function of the host can be influenced by the fungus present in the gut microbiome. Fungi may stimulate immune cells, including macrophages and dendritic cells, and they can also promote the generation of cytokines (Villena & Kitazawa, 2014). Studies have indicated that some fungus species, such *Candida albicans*, can trigger an immune system response that helps the body fight against bacterial infections (De Filippo *et al.,* 2010). Fungi in the gut microbiome also affect pathogen resistance. For instance, it has been discovered that *Candida tropicalis* inhibits the growth of potentially dangerous microorganisms, *Enterics almonella* (Yano *et al.,* 2015).

According to (Kim *et al.,* 2011) it has also been shown that the fungus species *Candida albicans* prevents the harmful bacterium *Staphylococcus aureus* from replicating. Fungi among the gut microbiome can aid in the absorption of nutrients. For instance, the fungus *Aspergillus niger* produces enzymes that enable the absorption of nutrients by dissolving complex polysaccharides (Hess *et al.,* 2011). Moreover, fungi can help produce some vitamins, including B vitamins (Sagheddu *et al.,* 2014). Fungi in the gut microbiome that serve as part of the gut barrier may contribute to its maintenance. For instance, it has been discovered that *Candida albicans* increases the synthesis of tight junction proteins, which support the integrity of the gut barrier (Middelkoop *et al.,* 2017) (Table 3).

Table 3: The human body's gut microbiome's functions

Types	**Description**
Digestion and Metabolism	Fungi help in the intricate metabolism and breakdown of carbohydratesIn the rumen of cows, for example, *Orpinomyces sp*. ferments lignocellulosic materials, whereas *Saccharomyces cerevisiae* breaks down dietary fibers in humans to produce energy-dense short-chain fatty acids.
Immune Metabolism	Immune system function is influenced by fungal interactions with the host's immune system. They may trigger the release of cytokines and activate immune cells like macrophages and dendritic cells. Specific species eliciting immunological responses, including *Candida albicans*, help to prevent bacterial infections.
Pathogen Resistance	The gut microbiome's fungi contribute to resistance to infections. Examples include the way in which *Candida albicans* prevents *Staphylococcus aureus* from replicating and *Candida tropicalis* restricts the growth of *Salmonella enterica*.
Nutrient Absorption	By producing the enzymes needed to break down complex polysaccharides, fungi aid in improved nutritional absorption. Fungi also aid in the manufacture of some vitamins, including the B vitamins.
Gut Barrier Function	By encouraging the synthesis of tight junction proteins and therefore improving the integrity of the gut barrier, certain fungi, such as *Candida albicans*, help to preserve the function of the gut barrier.

Detrimental impact of fungus in the gut microbiome on human health

A complex ecosystem of bacteria called the gut microbiome is essential to human health. Although research on the gut microbiome has traditionally concentrated on bacteria, recent findings have indicated that fungi also play a major role in gut health. A wide variety of microorganisms, fungi can have both beneficial and detrimental effects on human health, dependent on their quantity and composition within the gut microbiome.

Positive impacts on health

Immune system: Certain fungi in the gut microbiota can produce more cytokines and other immune molecules, which can help the body, fight off infections and inflammation. It has been demonstrated that certain *Saccharomyces bouvardia* strains enhance the function of the intestinal barrier and reduce inflammation (McFarland, 2010). The antimicrobial characteristics of According to Huang *et al*., (2020), certain gut fungus include antimicrobial compounds that can aid in the body's defence against harmful bacteria and other illnesses. Effects on mental health of since some evidence indicates that gut fungal imbalances may cause sadness, anxiety, and other mood problems, gut fungi may be beneficial to mental health. In addition, certain intestinal fungi produce neuroactive substances that alter behaviour and brain function.

Negative impacts on health

An inflammatory response in the stomach that can extend to other parts of the body can be brought on by an excess of certain fungus, such *Candida albicans*. Numerous medical conditions, such as cancer, heart disease, and autoimmune diseases have been linked to chronic inflammation (Scanlan & Marchesi, 2008). *Aspergillus* and *Fusarium* are only two of the many stomach fungus species that may infect people and notably weaken immune systems. These infections can be serious and sometimes fatal (Acharya & Bajaj, 2019). Imbalance in the gut fungus community has been related to a variety of digestive issues, including IBS, a condition known as inflammatory bowel disease, and constipation (Sam *et al.,* 2017). Some people are susceptible to fungus species in the gut, such as *Aspergillus* and *Penicillium*, which can cause mild to severe allergic reactions.

Disease susceptibility and the gut mycobiome

Historically, Because *Candida* species may be isolated using culture-dependent methods, it has historically been connected to a number various gut-related disorders such as inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), and gut inflammation reviewed by (Kumamoto, 2011). Researchers are also revealing the involvement of multiple fungi in the gut mycobiome regarding gastroenteritis utilising culture-independent approaches, and excellent reviews of the fungal microbiota and IBD may

be read (Richard *et al.,* 2015) (Mukherjee *et al.,* 2015). McKenzie *et al.,* (1990) discovered anti-*Saccharomyces cerevisiae* antibodies (ASCA) in CD patients, implying a function for the fungus in the inflammatory immune response in CD. Discovered the CD patients exhibited higher fungal richness and diversity than controls (Ott *et al*., 2014). Similar findings were made in another study by who discovered that CD patients' inflamed mucosa had a higher fungal diversity than non-inflamed mucosa (Li *et al.,* 2018). According to pervious research the CD patients have a different bacterial and fungal microbiota than healthy people, with fewer operational taxonomic units (OTUs), fewer Firmicutes, more Proteobacteria, and a higher fungal burden (Liguori *et al.,* 2015). A recent study of the microbiota of 235 IBD patients revealed a significant difference in alpha- and beta-diversity between healthy controls, UC patients, and CD patients, and while the beta-diversity clustering was weaker, the alpha-diversity of the fungal mycobiota was decreased in IBD patients compared to healthy controls Li *et al.,* (2014) & Sokol *et al.,* (2016) and other researchers observed *C. albicans* to be more prevalent in the IBD samples, similar to (Liguori *et al.,* 2015). IBD, a study that reviewed randomized controlled trials found significant effects of broad-spectrum antibiotics in the treatment of active CD and active UC (Pineton *et al.,* 2016). Taken together, these studies suggest that bacterial dysbiosis in the gut, and the richness and diversity of the mycobiome, are important in IBD susceptibility.

The fungal mycobiota is sensitive to disease states and interventions, frequently done histogenetically through therapy, and it reacts (directly or indirectly). Fungal compositions differ between DSS-induced colitis and normal conditions, as demonstrated in mice. In distinct gut regions of animals with DSS-induced colitis, fungal biodiversity was reduced in comparison to normal controls (Qiu *et al.,* 2015). Researchers discovered that anti-fungal treatment-induced fungal dysbiosis in mice led to the selection of uncommon, non-*Candida* fungus. This aggravated allergic airway illness and worsened the colitis brought on by DSS (Wheeler *et al.,* 2016). On the other hand, according to different research reviewed in researcher, revealed that patients who experienced antibiotic-associated diarrhea (AAD) had disturbed native microbiota before *Candida* overgrowth in the GI tract Krause & Reisinger 2005). Researchers discovered that the size of the adenoma and the stage of the illness in colorectal cancer affected the mucosal mycobiota (Luan *et al.,* 2015). In advanced adenoma biopsy samples, adenomas exhibited decreased variety and a notable enrichment of the group *Saccharomycetales*. Contrarily, *Fusarium* and *Trichoderma* genera were considerably enriched in the nearby rectal tissue samples as compared to non-advanced adenoma tissues (Luan *et al.,* 2015). This shows that the mycobiota may differ in accordance with the stage of the illness in patients with advanced adenomas. Even though this study only examined advanced adenoma and non-advanced adenomatous tissues, it showed variations in the mycobiota at various colorectal adenoma size stages. Future research is required to establish the cause and effect link between the mycobiota and colorectal cancer.

These dysbiosis studies show that the interplay between the microbiome and commensal fungus is a delicate balance; if the microbiome is frustrated, the typically commensal components of the mycobiome may go unrestrained and turn potentially hazardous.

Conclusion

The human digestive tract A microbiome is a complex ecosystem made up of millions of species such as bacteria, viruses, archaea, and fungus. Recent research has demonstrated that fungi play an important role in human health and can interact with other members of the microbiota and the host's immune system, regulating many physiological processes such as digestion, metabolism, and the immune system. Several variables influence fungal colonisation of the gut, including diet, antibiotics, and host genetics. Imbalances in the fungal population can cause inflammatory bowel disease, obesity, and type 2 diabetes, as well as impact the immunological system, resulting in autoimmune disorders and allergies. Therefore, Understanding the role of gut fungus in human health is thus crucial for finding innovative therapeutics for gut conditions. While research on Inter kingdom interactions (bacteria-fungi) in the gut is scarce, evidence shows that it plays an important role in influencing the microbial community's assembly and interaction with the host. More research is needed to fully understand the molecular mechanisms that mediate these interactions and their influence on human health.

Acknowledgments

I am thankful to Minhas Elahi, Asif Kamal, Momal Batool and Fazli Maula for their help in the manuscript writing, Atika Noor help in the proofreading of manuscript and the anonymous reviewers for their comments on the manuscript.

References

Arrieta, M.C., Arévalo, A., Stiemsma, L., Dimitriu, P., Chico, M.E., Loor, S. & Finlay, B. (2018). Associations between infant fungal and bacterial dysbiosis and childhood atopic wheeze in a non industrialized setting. *Journal of Allergy and Clinical Immunology*, *142*(2), 424-434.

Bernardes, V.T.E., Pettersen, V.K., Gutierrez, M.W., Laforest-Lapointe, I., Jendzjowsky, N.G., Cavin, J.B. & Arrieta, M.C. (2020). Intestinal fungi are causally implicated in microbiome assembly and immune development in mice. *Nature communications*, *11*(1), 2577.

Clancy, C.J., & Hong Nguyen, M. (2011). Systemic Candidiasis: Candidemia and Deep Organ Infections. *Candida and candidiasis*, 429-441.

De Filippo, C., Cavalieri, D., Di Paola, M., Ramazzotti, M., Poullet, J.B., Massart, S. & Lionetti, P. (2010). Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proceedings of the National Academy of Sciences*, *107*(33), 14691-14696.

Fan, D., Coughlin, L.A., Neubauer, M.M., Kim, J., Kim, M.S., Zhan, X., & Koh, A.Y. (2015). Activation of HIF-1α and LL-37 by commensal bacteria inhibits Candida albicans colonization. *Nature medicine*, *21*(7), 808-814.

Fiers, W.D., Gao, I.H. & Iliev, I.D. (2019). Gut mycobiota under scrutiny: fungal symbionts or environmental transients?. *Current opinion in microbiology*, *50*, 79-86.

Fujimura, K.E., Sitarik, A.R., Havstad, S., Lin, D.L., Levan, S., Fadrosh, D. & Lynch, S.V. (2016). Neonatal gut microbiota associates with childhood multi-sensitized atopy and T cell differentiation. *Nature medicine*, *22*(10), 1187-1191.

Ghannoum, M.A., Jurevic, R.J., Mukherjee, P.K., Cui, F., Sikaroodi, M., Naqvi, A. & Gillevet, P.M. (2010). Characterization of the oral fungal microbiome (mycobiome) in healthy individuals. *PLoS pathogens*, *6*(1), e1000713.

Hess, M., Sczyrba, A., Egan, R., Kim, T.W., Chokhawala, H., Schroth, G. & Rubin, E.M. (2011). Metagenomic discovery of biomass-degrading genes and genomes from cow rumen. *Science*, *331*(6016), 463-467.

Hui, W., Li, T., Liu, W., Zhou, C., Zheng, S. & Deng, X. (2020). Fungal microbiota, and host immunity in the context of intestinal infection. Front Microbiol; 11: 568720. doi:10.3389/fmicb.2020.568720.

Ihara, Y., Hirano, A., Endo, S., Kobayashi, H., & Torisu, T. (2019). Gastrointestinal: A case of zonisamide induced esophageal and small intestinal injury. *Journal of Gastroenterology and Hepatology*, *34*(10), 1671-1671.

Iliev, I.D., Funari, V.A., Taylor, K.D., Nguyen, Q., Reyes, C.N., Strom, S.P. & Underhill, D.M. (2012). Interactions between commensal fungi and the C-type lectin receptor Dectin-1 influence colitis. *Science*, *336* (6086), 1314-1317.

Khosravi, A. & Mazmanian, S.K. (2013). Disruption of the gut microbiome as a risk factor for microbial infections. *Current opinion in microbiology*, *16*(2), 221-227.

Koh, A.Y., Köhler, J.R., Coggshall, K.T., Van Rooijen, N. & Pier, G.B. (2008). Mucosal damage and neutropenia are required for *Candida albicans* dissemination. *PLoS pathogens*, *4*(2), e35.

Krause, R. & Reisinger, E.C. (2005). Candida and antibiotic-associated diarrhoea. *Clinical Microbiology and Infection*, *11*(1), 1-2.

Kumamoto, C.A. (2011). Inflammation and gastrointestinal Candida colonization. *Current opinion in microbiology*, *14*(4), 386-391.

Levine, J., Dykoski, R. K. & Janoff, E.N. (1995). Candida-associated diarrhea: a syndrome in search of credibility. *Clinical infectious diseases*, *21*(4), 881-886.

Li, Q., Wang, C., Tang, C., He, Q., Li, N. & Li, J. (2014). Dysbiosis of gut fungal microbiota is associated with mucosal inflammation in Crohn's disease. *Journal of clinical gastroenterology*, *48*(6), 513-523.

Liggenstoffer, A.S., Youssef, N.H. & Wilkins, M.R. (2014). Oxygen minimum zones harbor novel viral communities with low diversity. Environ Microbiol. 16(8):2659-2674.

Liguori, G., Lamas, B., Richard, M.L., Brandi, G., Da Costa, G., Hoffmann, T.W. & Sokol, H. (2016). Fungal dysbiosis in mucosa-associated microbiota of Crohn's disease patients. *Journal of Crohn's and Colitis*, *10*(3), 296-305.

Limon, J.J., Tang, J., Li, D., Wolf, A.J., Michelsen, K.S., Funari, V. & Underhill, D.M. (2019). Malassezia is associated with Crohn's disease and exacerbates colitis in mouse models. *Cell host & microbe*, *25*(3), 377-388.

Luan, C., Xie, L., Yang, X., Miao, H., Lv, N., Zhang, R. & Zhu, B. (2015). Dysbiosis of fungal microbiota in the intestinal mucosa of patients with colorectal adenomas. *Scientific reports*, *5*(1), 7980.

Markey, L., Shaban, L., Green, E.R., Lemon, K.P., Mecsas, J. & Kumamoto, C.A. (2018). Pre-colonization with the commensal fungus Candida albicans reduces murine susceptibility to Clostridium difficile infection. *Gut Microbes*, *9*(6), 497-509.

McKenzie, H., Main, J., Pennington, C.R. & Parratt, D. (1990). Antibody to selected strains of Saccharomyces cerevisiae (baker's and brewer's yeast) and Candida albicans in Crohn's disease. *Gut*, *31*(5), 536-538.

Middelkoop, T.B., Berrington, D.V. & Leeuwen, S.S. (2017). Fermentation of non-digestible rye bran and its fractions by the human gut microbiota in vitro. *J. Funct. Foods*; 32:242-251.

Morrison, D.J. & Preston, T. (2016). Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut microbes*, *7*(3), 189-200.

Mukherjee, P.K., Sendid, B., Hoarau, G., Colombel, J.F., Poulain, D. & Ghannoum, M.A. (2015). Mycobiotain gastrointestinal diseases. *Nature reviews Gastroenterology & hepatology*, *12*(2), 77-87.

Odds, F.C. (1987). *Candida* infections: an overview. *CRC Critical Reviews in Microbiology*, *15*(1), 1-5.

Revankar, S.G. & Sobel, J.D. (2011). Mucosal candidiasis. *Candida and candidiasis*, 417-427.

Richard, M.L. & Sokol, H. (2019). The gut mycobiota: insights into analysis, environmental interactions and role in gastrointestinal diseases. *Nature Reviews Gastroenterology & Hepatology*, *16*(6), 331-345.

Richard, M.L., Lamas, B., Liguori, G., Hoffmann, T.W. & Sokol, H. (2015). Gut fungal microbiota: the Yin and Yang of inflammatory bowel disease. *Inflammatory bowel diseases*, *21*(3), 656-665.

Sagheddu, V., Patrone, V. & Miragoli, F. (2014). Candida albicans promotes invasion and colonisation of gnotobiotic mice: role of ethanol and pH. PLoS One. 9(5): e98897.

Sam, Q.H., Chang, M.W. & Chai, L.Y.A. (2017). The fungal mycobiome and its interaction with gut bacteria in the host. *International journal of molecular sciences*, *18*(2), 330.

Santelmann, H. & Howard, J.M. (2005). Yeast metabolic products, yeast antigens and yeasts as possible triggers for irritable bowel syndrome. *European journal of gastroenterology & hepatology*, *17*(1), 21-26.

Scanlan, P.D. & Marchesi, J.R. (2008). Micro-eukaryotic diversity of the human distal gut microbiota: qualitative assessment using culture-dependent and-independent analysis of faeces. *The ISME Journal*, *2*(12), 1183-1193.

Seelig, M.S. (1966). Mechanisms by which antibiotics increase the incidence and severity of candidiasis and alter the immunological defenses. *Bacteriological reviews*, *30*(2), 442-459

Sokol, H., Leducq, V., Aschard, H., Pham, H.P., Jegou, S., Landman, C. & Beaugerie, L. (2017). Fungal microbiota dysbiosis in IBD. *Gut*, *66*(6), 1039-1048.

Sokol, H., Leducq, V., Aschard, H., Pham, H.P., Jegou, S., Landman, C. & Beaugerie, L. (2017). Fungal microbiota dysbiosis in IBD. *Gut*, *66*(6), 1039-1048.

Sovran, B., Planchais, J., Jegou, S., Straube, M., Lamas, B., Natividad, J.M. & Sokol, H. (2018). Enterobacteriaceae are essential for the modulation of colitis severity by fungi. *Microbiome*, *6*, 1-16.

Villena, J. & Kitazawa, H. (2014). Modulation of intestinal TLR4-inflammatory signaling pathways by probiotic microorganisms: lessons learned from Lactobacillus jensenii TL2937. *Frontiers in immunology*, *4*, 71145.

Vivarelli, M., Montalti, R. & Risaliti, A. (2013). Multimodal treatment of hepatocellular carcinoma on cirrhosis: an update. *World journal of gastroenterology: WJG*, *19*(42), 7316.

Wheeler, M.L., Limon, J.J., Bar, A.S., Leal, C.A., Gargus, M., Tang, J. & Iliev, I.D. (2016). Immunological consequences of intestinal fungal dysbiosis. *Cell host & microbe*, *19*(6), 865-873.

Yano, J.M., Yu, K., Donaldson, G.P., Shastri, G.G., Ann, P., Ma, L. & Hsiao, E.Y. (2015). Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*, *161*(2), 264-276.

Yapar, N. (2014). Epidemiology and risk factors for invasive candidiasis. *Therapeutics and clinical risk management*, 95-105.

Zhai, B., Ola, M., Rolling, T., Tosini, N.L., Joshowitz, S., Littmann, E.R. & Hohl, T.M. (2020). High-resolution mycobiota analysis reveals dynamic intestinal translocation preceding invasive candidiasis. *Nature medicine*, *26*(1), 59-64.