# Role of Yeasts in Healthy and Impaired Gut Microbiota: The Gut Mycome

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# Role of Yeasts in Healthy and Impaired Gut Microbiota: The Gut Mycome

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**Abstract:** Although several studies have been published on the gut microbiota composition, they are mainly focused on bacteria. Therefore, the world of gut yeasts, the "gut mycome", is still unclear. Over the last years, brand new gut microbiota analysis techniques have been applied to the study of yeasts, with exciting results both in health and in disease. A therapeutic potential for many gastrointestinal and extra-intestinal diseases has been recognized for selected yeast strains, such as Saccharomyces boulardii. This narrative review represents an overview of the new evidences regarding the "gut mycome".

**Keywords:** Gut mycome, gut microbiota, yeasts, *Saccharomyces boulardii*.

## INTRODUCTION

After birth the human gut is colonized by many microbial strains, often not cultivable with conventional methods. Dietary and environmental factors influence the development of a 'core native microbiome' that achieves stability during early life. Each individual has its specific gut microbiota that may change during the entire lifespan. The intestinal microbiota plays many fundamental roles, such as the protection of the gut against pathogenic strains, the development of a healthy immune system, the regulation of bowel motility and a great metabolic activity [1].

Gut microbiota composition has not been completely defined. Bacteria are certainly the most represented micro-organisms of the gut microbiota reaching more than 1 kg of weight and more than 1100 species. Bacteroidetes and Firmicutes usually are the predominant phyla in adult people, whereas Actinobacteria, or Proteobacteria are less common [2-3]. Bacteria are also the most studied component of gut microbiota: an electronic search on PubMed using the terms "gut microbiota AND bacteria" will give more than 2340 results (Table **1**);

The human microbiota also contains archaea, viruses (mainly bacteriophage), fungi and other Eukarya (as Blastocystis and Amoebozoa) [2], that are less studied than bacteria, as it can be easily seen searching each term on PubMed, as shown in Table **1**. However, these populations, yeasts in particular, may reveal a clinical significance, especially when an imbalance of gut microbiota occurs, such as after antibiotic therapies. Some of them, such as Saccaromyces boulardii, can also act as a therapeutic weapon in some particular cases.

The aim of this narrative review is to outline the role of yeasts in both healthy and unbalanced gut microbiota, and also to discuss their therapeutic significance.

## YEASTS IN HEALTHY GUT MICROBIOTA

Few evidences are available about the real amount of fungi in human gut microbiota. Candida strains are detectable in more than 95% of newborns after the first month of life [4]. On the other side, yeasts are detectable in the gut of about 70% of healthy adults [5], at different concentrations for each tract, with a growing gradient from mouth to anus (from $10^2$ at best in the stomach to a maximum of $10^6$ in the colon).

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**Table 1. The scientific weight, according to PubMed, of bacteria and yeasts linked to gut microbiota, and gut microbiota alone.**

| Search Terms | PubMedResults |
|---|---|
| "Gut microbiota" AND "yeasts" | 27 |
| "Gut microbiota" AND "bacteria" | 2340 |
| "Gut microbiota" | 2874 |

Most of these belong to Candida genus. Other yeasts and filamentous fungi can be found in stools, such as Aspergilli, Cryptococci, Trichospora, and other genera. Although some of them may be pathogenic in other organs (*i.e.*, lung), in the gastrointestinal tract they probably act as commensals, and most of them are transient in stools.

This enormous lack of knowledge may have in part a methodological reason: most of the studies have been performed using a culture-based approach, that usually does not own a good sensibility in detecting gut microbes from 60 to 80% of bacteria present in stools are undetectable with this method [6].

In the meantime new technologies have been developed and allowed a deeper, culture-independent analysis of gut microbiota composition. These techniques range from Polymerase-Chain-Reacton (PCR)-based methods, (*i.e.* Denaturing Gradient Gel Electrophoresis (DGGE) and Temperature Gradient Gel Electrophoresis (TGGE) procedures), to Fluorescent-In-Situ-Hybridization (FISH)-based methods, up to metagenomic studies, that represent the brand new approach to gut microbiota comprehension [7-8].

Some of these techniques have been applied also in studies regarding Eukarya and yeasts, with interesting results.

A Korean study has recently assessed the eukaryal diversity in human fecal samples by PCR-DGGE analysis of the 16S rRNA and 18S rRNA genes. Regarding eukaryal diversity, 11 of 17 sequences retrieved from the DGGE bands belonged to fungi. All sequences showed more than 97% sequence similarity to previously isolated organisms, e.g. Candida vinaria JCM 1813, Candida edaphicus CE1-01, Saccharomyces cerevisiae CICC1862$^T$, Saccharomyces servazzii ATCC$^T$. Briefly, the eukaryotic DGGE patterns revealed that the diversity of this eukaryal community was small (if compared to archaea and bacteria). Authors therefore concluded that the

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eukaryotic community (including yeasts) is more host-specific than the archaeal and bacterial ones [9].

Another study from Great Britain performed a qualitative assessment of the eukaryotic diversity of gut microbiota in 17 healthy volunteers, with both culture-dependent and –independent (based on DNA extraction and polymerase chain reaction targeting both the total eukaryotic 18S rRNA genes and fungal internal transcribed regions) methods of analysis. The assessment of the fungal populations highlighted important differences between data from the cultivable fraction, in which Candida species prevail, and from culture-independent techniques, where genera Gloeotinia/Paecilomyces and Galactomyces were most frequently retrieved [10].

Overall, these data confirm the power of culture-independent techniques revealing much more information than culture-based approach about gut microbiota composition.

Data about the functional role of fungal microbiota, especially in health, are lacking. Over the years, however, several functions have been hypothesized and analyzed, on the base of already existing evidences about bacteria.

The correlation between dietary patterns and bacterial lineages of gut microbiota has been extensively studied [11]. Recently, a relationship between gut yeasts and human diet has also been proposed: Candida genus has been positively associated to a carbohydrate-rich diet, and negatively associated to total saturated fatty acid. Since Candida is able to degrade starches, a role for Candida to assist in breaking down starch in carbohydrate rich foods has been proposed [12].

The comprehension of the relationship between yeasts and immune system is challenging: fungi are harder than bacteria to be distinguished from the self [13]. Yeasts are known to be harmful in individuals with impaired immunity: Candida albicans has shown to have a great ability to penetrate and injure immature enterocytes and to elicit IL-8 release [14], to produce amyloid that may inhibit the host neutrophil response [15], and has even been associated to autism [16].

However, a healthy immune system, with a working Th1 response (essentially driven by IL-12) should ensure the defense against yeasts [13].

Moreover, Candida albicans has been shown to modify the bacterial microbiota even during nonpathogenic colonization [17].

In mice the interactions between the commensal microflora and the gut immune system are critical for establishing a balance between immunity and tissue health. Fungi are recognized by a number of immune receptors among which Dectin-1 has emerged as key for phagocytosis and killing by myeloid phagocytes. Dectin-1 is a C-type lectin receptor that recognizes β-1,3-glucans found in the cell walls of nearly all fungi. Dectin-1 activates intracellular signals through CARD9 leading to inflammatory cytokine production and induction of T helper 17 (Th17) immune responses [18-21]. Deficiencies in either Dectin-1 or CARD9 result in enhanced susceptibility to pathogenic fungal infections in humans and mice [22-24].

Polymorphic variants in the gene for CARD9 are strongly associated with Crohn's disease and ulcerative colitis in humans [25-26]. Furthermore, anti- Saccharomyces cerevisiae antibodies (ASCA) against yeast mannan have been strongly associated with Crohn's disease [27-28]. Together, these later findings suggest a possible link between immune responses to commensal fungi and intestinal disease.

Iliev *et al*. showed that the mammalian gut contains a rich fungal community that interacts with the immune system through the innate immune receptor Dectin-1. Mice lacking Dectin-1 exhibited increased susceptibility t chemically-induced colitis, which was the result of altered responses to indigenous fungi. In humans it was identified a polymorphism in the gene for Dectin-1 (CLEC7A) that is strongly linked to a severe form of ulcerative colitis. Together these findings reveal a novel eukaryotic fungal community in the gut that coexists with bacteria and substantially expands the repertoire of organisms interacting with the intestinal immune system to influence health and disease [29]. Since the idea of probiotics as therapeutic resources has been established, several studies have been developed to investigate the role of selected yeast species, especially those isolated from food, such as Saccharomyces boulardii, in the preservation of the gut barrier [30-31].

However, the functional role of yeasts is still not well known. Therefore further researches targeted to this topic are necessary for a better understanding of the "gut mycome".

## YEASTS IN GUT MICROBIOTA IMPAIRMENT

The disruption of gut microbiota homeostasis may lead to several diseases. Since gut microbiota plays different roles in the gut, there will be many diseases related to the alteration of these functions. Yeasts have been shown to possess a role in gut microbiota-related diseases, by different points of view.

First, fungi can play a role in several diseases caused by an impairment of healthy gut microbiota, such as during inflammatory bowel diseases (IBDs).

Patients with Crohn's diseases and their relatives have shown to be more colonized by C. albicans than controls. A correlation of ASCA positivity and yeast colonization in relatives was also demonstrated, maybe resulting from an imbalanced immune response to C. albicans [32]. Metagenomics techniques, (18S rDNA-based DGGE, sequencing, clone libraries, and in situ hybridization techniques), have been applied to evaluate the composition of fungal microbiota, with interesting results. Forty-three different operational taxonomic units (OTUs) were found in clone libraries, all belonging to Ascomycota and Basidiomycota. A qualitatively different fungal microbiota was found between IBD patients and controls, and DGGE profiles showed a mean fungal diversity higher than controls in patients with Crohn's disease. However, no fungal species specific for CD and ulcerative colitis group were found. [33].

Furthermore, yeasts have been linked to chronic liver disease, that has recently been recognized to depend partially on gut microbiota imbalance. In particular, yeast could play a role in the natural history of HBV infection. In patients with different degrees of chronic HBV infection it was assessed an higher concentration of Candida spp. and Saccharomyces spp compared to healthy controls. Moreover, it was established an increased richness of yeast species in the hepatitis B cirrhosis group than in other patients, and the diversity of intestinal yeast microbiota, assessed through both culture-independent and culture-dependent methods, was positively correlated with the disease progression of chronic HBV infection [34].

On the other side, fungi act as saprophytes in the human gut, and the disruption of healthy gut microbiota by estrinsic factors (as immunosuppression, chemotherapy, or prolonged antibiotic treatment) could turn them in pathological entities.

Fungal flora of gastrointestinal tract has always been considered as a main source of infection and development of fungemia in immunocompromised patients [35]. A greater incidence of Candida species have been found in stool samples of children with hematological malignancies, in comparison with healthy patients [36].

Finally, gut microbiota impairment often depends on antibiotic overuse, and even yeasts are involved in this game. The normal gut flora can provide a 'natural' resistance to C. albicans, but it may be decreased by antibiotic therapy and enhanced by the use of probiotics [37]. Probably, this imbalance does not only affect the bacterial component of gut microbiota, but also the fungal population. Further studies, especially those with culture-independent techniques,

are needed to confirm this feeling, and to identify therapeutic targets.

## A THERAPEUTIC ROLE FOR YEASTS? THE CASE OF SACCHAROMYCES BOULARDII

Among the fungi there are some species that have a therapeutic potential. The most known is Saccharomyces boulardii (S. boulardii), a probiotic yeast which has shown several beneficial effects in humans [38-39]. S. boulardi acts as probiotic through different mechanisms of action with an antitoxin effect [40-41], a trophic action on the intestinal epithelium [42], and an antimicrobial activity [43-44], or through interaction with gut microbiota [45-46] or as a regulator of immune response [47-48]. S. boulardii was tested in many acute and chronic diseases. Several trials showed the effectiveness of the prophylactic use of S. boulardii in preventing antibiotic associated diarrhea [49-52]. In particular, the use of S. boulardii is recommended by the last Maastricht Guidelines as an adjuvant in reducing side effects of Helicobacter pylori antibiotic therapy [53-54]. A randomized, controlled, double blind trial [55] and a meta-analysis of six randomized controlled trials testing different probiotics showed significant efficacy of S. boulardii in preventing relapse of C. difficile infection in association with usual antibiotics (metronidazole or vancomycin) [56]. Furthermore, in two randomized controlled trials S. boulardii was more effective than placebo in reducing acute diarrhea in adult [57-58]. Another study showed that S. boulardii significantly reduced the incidence of traveler's diarrhea in a dose-dependent manner [59].

As other probiotics, S. boulardii was also tested in inflammatory bowel disease (IBD). A proof-of-concept study showed that, in a subset of patients unsuitable for steroid therapy with a mild to moderate clinical flare-up of ulcerative colitis, an additional treatment with S. boulardii during maintenance treatment with mesalazine achieved clinical remission in 17 of 24 subjects [60]. In Crohn's disease, a randomized controlled trial demonstrated a significant reduction in the mean of evacuation in the group treated with S. boulardii compared to placebo [61]. Another study showed the effectiveness of S. boulardii in the prevention of Crohn's disease relapses [62].

A randomized controlled trial assessed the efficacy of S. boulardii in reducing daily bowel movements in patients with irritable bowel syndrome and diarrhea (IBS-D) [63].

On the basis of these findings, S. boulardii can rightly be considered a viable therapeutic weapon for selected indications. Moreover, S. boulardii does not develop antibiotic and antifungal resistance [64] and does not persist in the gut more than 3-5 days from the first dose if the ingestion is interrupted [65]. Thanks to these characteristics S. boulardii has an excellent safety profile.

However, several cases of S. boulardii fungemia have been reported, especially in patients with severe comorbidities and with central venous catheters [66-67]. Hence, S. boulardii may result harmful in frail patients, and should not be administered during immunosuppression conditions, concurrence of antifungal therapy, in intensive care units, in severely ill subjects or in patients with a central venous catheters, to prevent the risk of fungemia [68-69].

## CONCLUSIONS

Few years ago, the fungal microbiota was a rarely explorated field of medical science. Probably this lack of knowledge was due to the difficulty of culturing yeasts and to their lower concentrations in the gut. However, the advent of new, culture-independent technologies has represented a step forward in the study of gut microbiota, mainly for bacteria and then yeasts.

Surely, a good knowledge of the real composition of gut mycome and of its functions in healthy people is needed for the understanding of related diseases and, moreover, of the therapeutic power of yeasts. Therefore, metagenomics studies on gut mycome, and studies investigating the relationships between bacteria, yeasts, and viruses in the gut lumen are strongly required.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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