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RESEARCH ARTICLE

SACCHAROMYCES CEREVISIAE AND THE FUNGAL EMERGENCY

[1*]Flores-Encarnación M., [1]Hernández-Hernández F.C., [2]Cabrera-Maldonado C., [1]Ocaña-Lozano D. and [3]García-García S.M.C.

[1]Laboratorio de Microbiología Molecular y Celular, Laboratorio 421 Edif. EMA1, Biomedicina, Facultad de Medicina, Benemérita Universidad Autónoma de Puebla, Puebla, Puebla, México; [2]Depto. De Microbiología. Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla, Puebla, Puebla. México; [3]Centro de Investigaciones Microbiológicas, ICUAP, Benemérita Universidad Autónoma de Puebla. Puebla, Puebla, México

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***Corresponding author:**
Flores-Encarnación M.,

ABSTRACT

As is known, in the last decade many emerging infectious diseases have become evident that have affected the world population. Bacterial and viral infections stand out, however there are infections caused by various fungi that are today considered emerging pathogens. Among the emerging pathogenic fungi, we can mention the case of *S. cerevisiae*, a yeast that has been used since time immemorial, for example for the manufacture of bread or some fermented drinks. Thus, this work shows some important aspects in relation to *S. cerevisiae* as an emerging pathogenic fungus.

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INTRODUCTION

Immunosuppression is an important factor in defining the fungal infection. The increase in the number of susceptible individuals, mainly due to AIDS, chemotherapy and organ transplantation, diabetes and autoimmune diseases, and treatment with broad-spectrum antibiotics or invasive medical procedures, as well as a recently identified group of patients with COVID-19, who received corticosteroids/ immunosuppressant drugs, contributed to the significant increase in the global incidence of invasive fungal infections over the last 50 years (Corrêa-Moreira *et al*., 2014; Hoenigl *et al*., 2022; Loh and Lam, 2023). So, increasing numbers of immunosuppressed individuals has led to a significant increase in the incidence of opportunistic infections, particularly those caused by fungi. The epidemiology of infections caused by the fungal pathogens such as *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus*, has been well documented. However, a number of species, which have previously been unrecognized or have previously been assumed to be non-pathogenic, for example *C. dubliniensis*, *Scedosporium* spp., *Fusarium* spp., *Saccharomyces cerevisiae* and others, that have emerged as agents of human diseases (Hazen, 1995; Perfect and Schell, 1996; Pontón *et al*., 2000). Therefore, this work shows the most relevant aspects of damage caused by *S. cerevisiae* as a current emerging pathogen.

CURRENT EMERGING FUNGAL INFECTIONS

Fungal infections are an important cause of morbidity and mortality among hospitalized patients around the world. While most invasive fungal infections are caused by *C. albicans*, *Aspergillus* spp., *Cryptococcus* species and the dimorphic fungi, other fungal species are emerging as important pathogens among immunocompromised patients (Beck-Sague and Jarwis, 1993; Hazen, 1995; Perfect and Schell, 1996; Pontón *et al*., 2000; Rees *et al*., 1998). At the end of the 20th century, hospital-acquired fungal infections were on the rise. Yeast infections of the genus *Candida* have become one of the most common causes of bloodstream infections. The increase in fungal infections is generally attributed to greater survival of immunocompromised people, as well as the increase in the number of people who are hospitalized for prolonged periods

or who are subjected to immunosuppressive therapy, catheterization, the use of broad-spectrum antibiotics, among others (Banerjee *et al*., 1991). This alarming increase in nosocomial fungal infections has alerted clinicians and scientist that yeasts, previously thought innocuous and relegated to plant pathology or industrial use, were capable of causing serious illness (Corrêa-Moreira, 2024). Three groups of fungal pathogens caused co-infections in COVID19: *Aspergillus* species, *Mucor*and *Candida* species, including *Candida auris*. Coronavirus disease 2019 (COVID-19)-associated invasive fungal infections are an important complication in a substantial number of critically ill, hospitalized patients with COVID-19 (Hoenigl *et al*., 2022). The first cases of COVID19-associated pulmonary aspergillosis were reported from China in early 2020. Since then, multiple case series and cohort studies have highlighted the importance of this potentially life-threatening secondary infection, sometimes caused by azole-resistant *Aspergillus* spp. The most commonly affected patients are those with acute respiratory failure due to COVID-19, particularly patients receiving systemic corticosteroids or tocilizumab therapies (Arastehfar *et al*., 2020; Bartoletti*et al*., 2021; Feys *et al.,* 2021; Janssen *et al.* 2021; Koehler *et al*., 2020; Permpalung *et al*., 2022; Prattes *et al.*, 2022; Salmanton-García *et al*., 2021; White *et al*., 2021; Yang *et al*., 2020). On the other hand, it has been reported that *S. cerevisiae* is an ubiquitous fungus that rarely infects humans. However, it has been reported that this yeast can cause infections consisting of pneumonia, urinary tract infections, liver abscess, and it has been associated with endocarditis. It has also been observed that most of the *S. cerevisiae* infectivity came from intravascular catheters and from prolonged antibiotic therapy (Aucott*et al.,* 1990; Enache-Angoulvant and Hennequin, 2005; Nawaz *et al*., 2022). Below are some relevant aspects of the yeast *S. cerevisiae* and its impact on human health.

USES OF *S. cerevisiae:* *S. cerevisiae* has been an essential component of human civilization because of its extensive use in food and beverage fermentation in which it has a high commercial significance. *S. cerevisiae* is a model organism in many aspects of basic research and in a variety of industrial applications. This yeast is characterized because, even under aerobic conditions, it does not use the respiratory machinery to metabolize saccharides and promote biomass, but instead produces ethanol and other two-carbon compounds through pyruvate. Thus *S. cerevisiae* produces and accumulates ethanol, which is toxic to most other microbial species capable of competing for sugar compounds. This mechanism eliminates microbial competition by cleaning the ecological niche, especially its competitors; then *S. cerevisiae* consumes the ethanol produced for its own growth. This lifestyle is called the "make-accumulate-consume" or Crabtree effect (Parapouli *et al*., 2020; Pronk *et al*., 1996; Thomson*et al.,* 2005). *S. cerevisiae* has also been found in the environment. The study of environmental strains has shown that they have additional survival strategies compared to industrial or laboratory strains. Such strategies in environmental *S. cerevisiae* strains are attributed to more stressful growth conditions than laboratory ones, as an example, environmental *S. cerevisiae* strains can overwinter in soil where they can sporulate. Other known natural niches of *S. cerevisiae* are leaves and trunks of various plant species, such as oaks. *S. cerevisiae* has been found in abundance in wineries (Parapouli *et al*., 2020*). S. cerevisiae* can occupy an additional niche: insects. This yeast is transmitted by insects. This has been detected in several insects, such as wasps and *Drosophila* species, which feed on damaged grapes (Buser *et al.,* 2014; Parapouli *et al*., 2020; Stefanini *et al*., 2012). *S. cerevisiae* is involved in the production of many fermented beverages, such as wine, beer and cider; distilled beverages, such as rum, vodka, whisky, brandy, and sake; whereas in other alcoholic beverages worldwide, from fruits, honey, and tea, *S. cerevisiae* is also involved (Stewart, 2014). *S. cerevisiae* is involved in the production of bread. The practice of bread making is one of the oldest biochemistry processes in the world. There are strong indications that yeast was already used in 10,000 BC to produce bread but the earliest archaeological evidence for leavened breads was found in the second millennium BC in Egypt and the first millennium BC in North Western China. Until the middle ages bread was mostly made at home, but during the population expansion of the 11th and 12th centuries, communal mills and ovens were constructed and professional bakers became common (Carbonetto *et al*., 2018; Heitmann *et al*., 2018; Joseph and Bachhawat, 2014; Nielsen, 2019; Money, 2018). On the other hand, *S. cerevisiae* var. *boulardii* as a probiotic helping to restore normal gut microbiota in patients after antibiotic therapy or surgery has been used. *S. cerevisiae* can temporarily function as a replacement for the natural microbiome until it is restored. *Saccharomyces*, is a very common composition of probiotics used in the intensive care unit for the treatment of antibiotic associated diarrhea, *Clostridium difficile* infection and irritable bowel síndrome (Gupta *et al*., 2019). Various mechanisms such as modulation of the normal intestinal microbiome, antagonism against pathogens, adhesion to mucus, modulation of the immune system and trophic effects in the gastrointestinal tract, have promoted the probiotic action of *S. cerevisiae* (Kelesidis and Pothoulakis, 2012; Pais *et al*. 2020; Staniszewski and Kordowska-Wiater, 2021). Yeast are advanced fungi of division Ascomycetes, class Saccharomycetes which grow as single cell and includes *Candida* and *Saccharomyces*. *Saccharomyces* and *Candida* are both a part of the normal flora of airway and gut in humans (Gupta *et al*., 2019). Applicability of *S. cerevisiae* as a biocontrol agent of *Fusarium oxysporum* and as plant growth promoter was also investigated. Due to its cytokinin content, yeast treatments were suggested to play a beneficial role in cell division and cell enlargement (Natio *et al.,* 1981).

***S. cerevisiae* AS AN EMERGING OPPORTUNISTIC PATHOGEN:** *S. cerevisiae*, a close relative of the pathogenic *Candida* species, is an emerging opportunistic pathogen. Therefore, it is common to find *S. cerevisiae* in different parts of the body and clinically, in different types of patients as it is an emerging opportunistic pathogen. Unlike laboratory *S. cerevisiae* strains and other non-clinical strains, *S. cerevisiae* strains from clinical isolates have characteristics that resemble those found in pathogenic fungi, such as profuse pseudohyphal formation and growth at high temperatures. In experimental infections, clinical isolates and clinically derived strains of *S. cerevisiae* have also been shown to proliferate and persist in exogenously immunocompetent (CD-1) mice and kill complement factor five-deficient mice (Byron *et al.* 1995; Clemons *et al*. 1994; Goldstein *et al.,* 2001; Hazen, 1995; McCusker *et al.* 1994; Murphy and Kavanagh, 1999). *S. cerevisiae* is an ascospore-producing yeast, it is an occasional commensal on human mucosal surfaces and is not uncommon in clinical samples. It is rarely associated with serious human infections.

Data from the literature reported 8 cases of potentially serious *S. cerevisiae* infections, including 6 fungemias, one peritonitis, and one pleural effusion. Although three of the eight patients died, infection with *Saccharornyces* spp. was not the primary cause of death in two of these cases as one patient died from complications of disseminated intravascular coagulopathy and the other died from an insulin reaction. *S. cerevisiae* have also been associated with genitourinary infections in both men and women as well as mild gastrointestinal and respiratory infections (Eng *et al.*, 1984; Kiehn *et al.,* 1980; Tawfik *et al*., 1989; Wilson *et al.,* 1988). *S. cerevisiae* (*boulardii*) fungemia was first reported in 1970 in a patient with a prosthetic mitral valve. Since then, many other fungemia cases caused by this yeast have been reported. Although *S. cerevisiae* (*boulardii*) is considered a safe and non-pathogenic biotherapeutic agent several reports show that this fungus may cause severe infections. Probiotics are often regulated as dietary supplements rather than as pharmaceuticals or biological products. The most important area of concern with probiotic use is the risk of sepsis. There are several cases of systemic infections related to probiotic treatment with *S. boulardii*, including unexplained fever, fungemia, endocarditis, pneumonia, liver abscess, peritonitis and septic shock. *Saccharomyces* infection is clinically indistinguishable from invasive candidiasis. Thus, critically ill patients are special cases to be evaluate before the decision of probiotic treatment (Cohen *et al*., 2016; da Silva *et al*., 2011; Ellouze *et al*., 2016; Herbrecht and Nivoix, 2005; Kara *et al*., 2018; Lherm *et al.,* 2002; Lolis *et al.,* 2008; Martin *et al.*, 2017; Santino *et al.*, 2014; Stefanatou *et al*., 2011; Thygesen *et al*., 2012). As is known, *S. cereviciae* infection occurs more frequently in immunocompromised patients and causes frequently fungemia.

Elkhihal *et al.*, (2015) reported the case of an adult diabetic patient with a urinary infection due to *S. cerevisiae*. The disease began with burning during urination associated with frequent urination without fever. The diagnosis was established by the presence of the yeast on fresh examination and the positivity of the culture on Sabouraud-chloramphenicol. The administration of probiotic preparations containing live yeasts (such as *Saccharomyces*) may posea high risk for patients who suffer from immune deficiencies, malignant diseases or who are being treated with immunosuppressants. Therefore, the main route of entry for invasive *S. cerevisiae* infections is the oral route. It has also been observed that oral ulcers can cause the translocation of yeast into the bloodstream in these patients. Acquisition of *S. cerevisiae* can be nosocomial. In this case, the yeasts can be located on the surfaces of the rooms or spread up to a distance of 1 m after opening the capsules when the administration is carried out (nasogastric tube). *S. cerevisiae* has also been detected on the hands of medical personnel. Another entry route is the use of central venous catheters in critically ill patients, representing a form of manual transmission (Cassone *et al*., 2003; Enache-Angoulvant and Hennequin, 2005; Hennequin *et al*., 2000; Sulik-Tyszka *et al*., 2018; Tomblyn *et al.*, 2009; Ventoulis *et al*., 2020). Finally, *S. cerevisiae* is generally identified as a harmless and friendly yeast for humans, however, as mentioned above, this yeast can be responsible for disease in different organs, mainly in immunosuppressed people. As *S. cerevisiae* is a microorganism widely used in the food industry, more studies should be carried out on these yeasts since they have been the cause of clinical infections (Morard *et al*., 2023).

CONCLUSION

Fungal infections have become a major health problem, especially infections associated with people with immune system deficiencies. In this sense, *S. cerevisiae*, which has always been considered a non-pathogenic fungus, is one of the fungi that has been isolated as a causal agent of various infectious processes such as pneumonia, skin conditions, fungiemia, etc. The main route of entry for this yeast has been oral as it is used as a probiotic and due to its presence in many food products.

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