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Review

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Emergence of *Saccharomyces cerevisiae* as a human pathogen Implications for biotechnology

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Abstract

The yeast *Saccharomyces cerevisiae* is widely used in baking, brewing, wine making, and biotechnology and previously has had GRAS (generally regarded as safe) status. Recent evidence indicates the involvement of *S. cerevisiae* in a range of superficial and systemic diseases. Numerous cases of *S. cerevisiae*-induced vaginitis have been documented as have cases of oropharyngeal infection. Potentially fatal systemic disease due to *S. cerevisiae* has been recorded in bone marrow transplant patients and in those immunocompromised as a result of cancer or AIDS. A number of studies have indicated that commercially available strains of *S. cerevisiae* may cause disease in certain individuals. Pathogenic isolates exhibit the ability to grow at 42°C, produce proteinase, and are capable of pseudohyphal growth. In addition, a number of isolates are capable of phenotypic switching and show partial or complete resistance to commonly used antifungal agents, including fluconazole. In the light of these findings, *S. cerevisiae* should now be regarded as an opportunistic pathogen, albeit of relatively low virulence, and treated accordingly by those in the industrial and biotechnological sectors.

Keywords: *Saccharomyces*; Emerging pathogen; Biotechnology

1. *Saccharomyces cerevisiae*: friend or foe?

The saprophytic yeast *S. cerevisiae* is widely distributed in nature and has been used extensively since the dawn of civilization. Until recent times the primary use of this yeast has been in the production of bread (baker's yeast) and alcoholic beverages (brewer's yeast). It is also frequently ingested as a dietary supplement or inadvertently as a contaminant of food products.

S. cerevisiae has become increasingly important over recent years in biotechnology and is now one of the most studied and best characterized organisms on the planet. It has been used as a model eukaryote for some time and is an excellent model for studies on mitochondrial form and function. *S. cerevisiae* has been used extensively in the biotechnology sector as a cloning vector (single or multicopy). One advantage of using *S. cerevisiae* is that proteins can be secreted into the growth medium or anchored in the cell wall of the yeast, as in the case of the α-galactosidase-α-agglutinin (αGal-AC1) fusion protein [1]. The amount of fusion protein present on the yeast cell surface is dependent on the copy number of the construct used. *S. cerevisiae* is used to produce small hepatitis B surface proteins for use in hepatitis B vaccines, and production of the proteins is highest for those cells containing a high multicopy plasmid [2]. *S. cerevisiae* is also used to mass-produce the interferon class of immune cytokines, which are important in the regulation of immune responses to certain diseases. For example, interferon α is important in the treatment of certain cancers, in particular lymphomas such as Kaposi's sarcoma [3,4], and interferon γ is used in combination with antimicrobials in order to prevent the recurrence of some infections [5,6].

There are many reasons for the widespread use of *S. cerevisiae* in the biotechnology sector. Culturing the yeast is inexpensive and relatively easy. *S. cerevisiae* has always had "generally regarded as safe" status and can, therefore, legally be used in the food and pharmacological sector [1]. However, numerous cases of clinical infection caused by *S. cerevisiae* have been reported in the literature in recent years. Classically, *S. cerevisiae* has been regarded as nonpathogenic, but recent evidence indicates that some isolates

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are virulent and have been implicated in the induction of disease, particularly in immunocompromised individuals. In Europe, *S. cerevisiae* has been upgraded from "generally regarded as safe" to Biosafety level one [7], indicating the ability to cause superficial or mild systemic infections. This finding will have profound implications for the continued use of this yeast, particularly in situations where prolonged contact with susceptible hosts is a possibility. *S. cerevisiae* should now be regarded as an opportunistic pathogen of low virulence rather than as a nonpathogenic yeast.

This review will examine cases of *S. cerevisiae*-induced disease, identify the virulence factors of pathogenic isolates, and discuss the ability of the yeast to resist conventional antifungal agents. Current therapy and possible future alternatives will be examined. The potential dangers and implications of the continued use of *S. cerevisiae* in the biotechnology sector will be assessed.

2. *S. cerevisiae*-induced disease

Although frequently encountered as a harmless body, commensal *S. cerevisiae* has been implicated in the induction of disease in a number of instances. It would appear that *S. cerevisiae* is exploiting the increased numbers of patients immunocompromised as a result of disease or therapy rather than exhibiting enhanced levels of virulence. A review of the medical literature indicates that *S. cerevisiae* isolates have been responsible for a variety of diseases ranging from superficial to life-threatening, systemic infections. Infections due to *S. cerevisiae* have been recorded in patients showing no obvious predisposing factor(s) [8,9] but also in those severely immunocompromised as a result of disease (e.g. AIDS, malignancy, diabetes) or therapeutic procedure(s) (e.g. broad spectrum antibiotic therapy, organ transplantation). The reported extent of *S. cerevisiae*-induced disease is probably an underestimate of the true situation due to a continuing belief by many in the medical profession that this yeast is nonpathogenic [8]. In addition, there is a tendency to arbitrarily identify any yeast isolated from clinical samples as belonging to the genus *Candida* rather than pursuing the identification to reveal the real culprit [9,10].

3. Superficial *S. cerevisiae* disease

Yeast-induced vaginitis affects approximately 75% of women at some point in their life, and a subpopulation of between 5% and 12% suffer from recurrent bouts of infection that may persist for months or, in severe cases, years [11]. *Candida albicans* is responsible for 85–90% of cases of this condition, with the remaining cases being due to a range of other *Candida* species. In a survey of the yeasts responsible for this condition in 2000 women, *S. cerevisiae* was identified as the causative agent in only nine cases (0.45% of the sample population) [9], and another survey reported an incidence of 1.06% in a patient population of 750 [12]. Other reports have identified *S. cerevisiae* as the etiologic agent in 0.45–0.7% of cases [11,13]. One study identified the presence of *S. cerevisiae* in 5.4% of women presenting with symptoms of vaginitis and in 19.7% of asymptomatic women [14]. Although it must be stated, there was no evidence in this case that *S. cerevisiae* was the sole yeast responsible for the condition. In many cases where vaginitis was caused by this yeast, recurrent bouts of infection were noted. It was also observed that *S. cerevisiae* was frequently isolated in association with *Candida glabrata*, another vaginal pathogen, or following a bout of vaginitis induced by this latter yeast that may indicate that the two yeasts coexist as pathogens in the vagina [9]. Patients presenting with *S. cerevisiae*-induced vaginitis showed no apparent predisposing factors, while a number of patients had local disease or other predisposing conditions that may have facilitated the growth of the yeast [9].

While *S. cerevisiae* may be found as a normal component of the gastrointestinal tract in humans, and transmission from this site to the female genital tract may occur, exogenous infection with *S. cerevisiae* has been documented. *S. cerevisiae*-induced vaginitis has been recorded in women whose partners worked in bakeries or pizzeria. Electrophoretic karyotyping of yeasts isolated from the vagina, the hands of the patient's husbands, and the yeasts used in the pizzeria revealed the presence of the same strain [12]. It was suggested that overexposure to this yeast resulted in vaginal colonization and infection. There are no reports in the literature of cases of *S. cerevisiae*-induced vaginitis in women working in bakeries who would be exposed to huge amounts of the yeast on a daily basis, although this condition has been linked to the use of *S. cerevisiae* in home baking [13].

Restriction enzyme analysis of isolates of *S. cerevisiae* responsible for vaginitis by using *Eco*RI indicated that genetically indistinguishable isolates were responsible for infection in nonrelated groups of women [13]. A number of strains were identical to yeasts commercially available for baking, again indicating the possibility of exogenous infection of the vagina. Some *S. cerevisiae* isolates implicated in the induction of vaginitis could be divided into two subtypes based upon the presence or absence of a 3-kb fragment upon agarose gel electrophoresis [15].

4. Systemic *S. cerevisiae* disease

S. cerevisiae-induced vaginitis may be unpleasant, and at times difficult to treat due to the inherent drug resistance of certain isolates, but it is not life threatening except in severely immunocompromised patients where systemic infection may result. Systemic fungal disease due to *S. cerevisiae* has been recorded occasionally and is most frequently found in severely ill patients and may be a contributer to, or in some cases the main cause of, death. *S. cerevisiae* has been implicated in pneumonia in a HIV+ patient, and the pres-

ence of this organism in a number of organs at autopsy was recorded, leading to the suggestion that the yeast first colonized the oropharynx of the immunocompromised host and was then aspirated to the lungs, where it entered the bloodstream and spread hematogenously to the spleen and small intestine [16].

In three cases of invasive infections with *S. cerevisiae*, pneumonia, liver abscess and sepsis, and systemic infection were attributed to the presence of this yeast [17]. *S. cerevisiae* was isolated from a number of organs and from sites that would normally be regarded as sterile, indicating that pathogenic isolates of this yeast are capable of tissue invasion and dissemination. A female patient who underwent bone marrow transplantation (BMT) developed a fever, and blood cultures revealed the presence of *S. cerevisiae* [18]. Although this is the sole reference to *S. cerevisiae* infection in BMT patients, it does indicate that this yeast is capable of infecting patients immunocompromised as a result of therapeutic procedures. *S. cerevisiae* septicemia in a patient with preleukemic hemopathy may have been responsible for death [19], and *S. cerevisiae* has also been associated with cases of septicemia [20] and postoperative peritonitis [21]. While the involvement of *S. cerevisiae* in a range of superficial and systemic diseases has been well documented, there is some evidence to suggest that the yeast may also play a role in the induction of Crohn's disease. Elevated levels of IgG and IgA antibodies to *S. cerevisiae* have been detected in patients affected by Crohn's disease, but any involvement of this yeast in the etiology of this condition remains to be clarified [22].

S. cerevisiae has been implicated in a range of diseases in geriatric patients and those immunocompromised as a result of disease. The number of cases of infection by this yeast in such patients is still relatively low, especially when compared to cases caused by *C. albicans*, but the salient fact is that infection is caused by what was previously regarded as a nonpathogen. In one case, a patient was admitted to the hospital for hypotension, shortness of breath, and chest pain. The patient had a number of predisposing factors and was on a "health diet" consisting of a large daily intake of vitamins and brewer's yeast. *S. cerevisiae* was isolated from the lungs, and the ingestion of baker's yeast was identified as the source of infection [23]. The ingestion of brewer's yeast has previously been associated with fever [24]. In addition to entry via the oropharynx, gastrointestinal tract, and indwelling cathethers, the ingestion of food contaminated with *S. cerevisiae* is considered a potential source of infection in BMT patients [18].

The yeast *Saccharomyces bouladrii* (nom. inval) has been administered for the treatment of severe cases of diarrhea but cannot be genotypically distinguished from *S. cerevisiae* [25], and a number of cases of fungemia have been documented following the use of this yeast to control diarrhea. Analysis of commercially available strains of *S. boulardii* has revealed moderate virulence levels when tested in murine models of systemic infection [13]. Consequently, caution is recommended when using this yeast to control this condition in severely ill or immunocompromised patients.

5. Virulence attributes of pathogenic *S. cerevisiae* isolates

Virulent isolates have been defined as those isolates of *S. cerevisiae* that are capable of growth at 42°C [26]. This is considered an important characteristic as febrile patients can manifest this temperature, and any organism that can survive and grow at this elevated temperature would have an inherent advantage. In an examination of a range of laboratory and industrial strains of *S. cerevisiae*, growth was observed over the range 37–40°C, but only virulent isolates were capable of growth at 42°C. The ability to grow at this temperature appears to be critical to the virulence of *S. cerevisiae* and seems to be polygenic in nature. Some clinical isolates also demonstrate the ability to produce and secrete proteinase, as determined by the ability to liquefy gelatin and hydrolyse casein. The pathogenic yeast *C. albicans* can also secrete proteinases that have been implicated in the degradation of immunoglobulin A (IgA), an important element of the host's immune response to infection by this yeast [27]. Virulent isolates may grow as pseudohyphae under certain conditions, and pseudohyphae have been seen to penetrate agar, which may give an indication of their role in vivo [28]. Pseudohyphal growth was not observed in nonclinical isolates of *S. cerevisiae*, and this ability may be important in the penetration of host tissue by virulent isolates and could play a role in the blocking of capillaries associated with animal mortality [29].

Clinical isolates of *S. cerevisiae* persisted in the brains of CD-1 mice for up to 7 days, but nonclinical isolates were cleared, indicating that pathogenic isolates can grow and avoid clearance in immunocompromized animals [29]. Complement factor five-deficient mice were inoculated intravenously, and the presence of *S. cerevisiae* in the brain, spleen, liver, kidney, and lung was recorded. By using this model system, *S. cerevisiae* isolates were differentiated into four categories on the basis of tissue penetration, persistence, and mortality [8]. One group of isolates gave a mortality rate in excess of 80%, and the second produced an intermediate mortality rate (30–80%). The third class of isolates were described as being of low virulence; they produced low or negligible mortality but did proliferate to high levels in the brain. The fourth class were deemed to be nonvirulent, did not kill, and did not persist for long periods in inoculated animals. The persistence of the yeasts in the brain, spleen, liver, kidneys, and lungs depended upon the nature of the isolate (virulent vs. nonvirulent) but many were still present at certain body sites 14 days postinfection, indicating the ability of this yeast to perisist for long periods in immunodeficient animals and grow in environments that it would not normally encounter.

Phenotypic switching is a well-characterized phenomenon in the pathogenic yeast *C. albicans* where it has been implicated in the generation of variant phenotypes in infecting populations [30,31]. This phenomenon has also been observed in virulent isolates of *S. cerevisiae* where it occurs at a high frequency and does not require mutagenesis [32]. It is different from the well characterized phenotypic switch seen in *S. cerevisiae* (grande/petite) in that it is reversible and occurs at a high frequency. It may act as a virulence factor in that it allows the rapid generation of variant phenotypes in an infecting population, but the role of phenotypic switching in the virulence of *S. cerevisiae* has yet to be established. Some clinical isolates have demonstrated the ability to flocculate under in vitro conditions, and this may constitute a virulence factor in that it could lead to the obstruction of capillaries; however, no clear correlation with pathogenicity has yet been established [8]. The role of heat-shock proteins in the pathogenesis of *S. cerevisiae* has been investigated, and it has been established that overexpression of heat-shock protein 90 increases virulence in mice [33]. This protein is an immunodominant antigen and is associated with protective humoral immunity.

In summary, virulent isolates of *S. cerevisiae* manifest a number of characteristics which are essential for their pathogenicity in the human host. They are capable of proliferating within the host, particularly if the host is immunocompromised as a result of therapy or disease, and may persist for prolonged periods of time in susceptible hosts. Virulent isolates have also been shown to be capable of dissemination from the site of entry and of invading tissue.

6. Therapy for the control of *S. cerevisiae* disease

There are two major classes of antifungal agents: the polyenes and the azoles. Amphotericin B desoxycholate is the primary polyene for use against fungal infections and is produced by the *Streptomyces*. It is quite similar to a phospholipid in structure and length except that it contains a polyene hydrocarbon backbone as well as a polyhydroxyl backbone [34]. The drug is poorly soluble in water [35] due to the opposite polarities of the hydroxyls and hydrocarbons [34] and is conventionally dissolved in sodium desoxycholate solution [36], leading to the production of ribbon-like micelles.

The azole class of antifungal agents are synthetic drugs not found in nature. They contain three azole groupings and act by inhibiting ergosterol biosynthesis, which is achieved by blocking the conversion of lanosterol to 14α-demethyllanosterol and leads to the accumulation of ergosterol precursors [37] and subsequent disruption of membrane integrity. Therapy with azoles can be orally or topically administered [11].

In a number of cases where amphotericin B desoxycholate was successfully used to treat *S. cerevisiae* infection, all but one resulted in the cure of disease [16,17]. Amphotericin B was used to treat *S. cerevisiae* found in the lung, blood, urine, and in a liver abscess, indicating the usefulness of the drug in treating infections in a wide range of anatomical areas. On this basis, it was recommended that amphotericin B should be the treatment of choice for *S. cerevisiae* infection [17]. However, as has previously been noted, *S. cerevisiae* infection has been particularly associated with immunocompromised individuals. Amphotericin B is a very powerful antifungal agent that has been in use for over 40 years, but its usefulness is limited due to its well documented adverse effects on the renal system [38–41]. Amphotericin B functions by binding to sterols in the cell, and its efficacy is achieved by its affinity for ergosterol in fungal cell membranes causing pore formation and leakage of the cells' contents. It is believed that the binding of the drug to cholesterol in mammalian cell membranes [38] is responsible for amphotericin B toxicity. The renally toxic nature of amphotericin B precludes many individuals from receiving it and also causes many others to cease therapy due to side effects. Infusion-related side-effects, such as chills and fevers, are usually resolvable through clinical management [38,41]. Renal side-effects include inability to concentrate urine (leading to electrolytic imbalance), causing either dose reduction or termination of the therapy [41]. Renal tubular damage is also quite common and severe [40,41].

Amphotericin B is not always an option in treating *Saccharomyces* infection due to the adverse side effects associated with its use, but many other agents, particularly the azole antifungals, have been used to treat such infections. Fluconazole has become the treatment of choice for many types of *Candida* infections. In one case report, the use of 150 mg/day of fluconazole cured a patient with *Saccharomyces* infection [18]. Previously, however, outright resistance to fluconazole during in vitro antimycotic testing was recorded [9]. These results were borne out by the use of fluconazole in the treatment of a 38-year-old female patient with *S. cerevisiae* vaginitis. This patient was treated with 200 mg/day for 7 days. This therapy failed, and the patient went into remission following treatment with clotrimazole 100 mg/day followed by 500 mg/week. There was prompt clinical response during the first 7 days of clotrimazole treatment in contrast with the fluconazole treatment.

Clotrimazole therapy led to cure in two cases of *Saccharomyces* disease [9], but the response in both cases was slow, and eradication of the yeast occurred only after prolonged therapy. Ketoconazole at 400 mg/day for 14 days was then used to eradicate the yeast after cultures were found to be positive. This treatment failed, and clotrimazole was again used at 100 mg/day until total eradication was achieved. Follow-up therapy of clotrimazole at 500 mg/week eventually led to remission.

Ketoconazole has been used to treat *S. cerevisiae* infections with varying rates of success. Ketoconazole (200 mg) was administered orally, twice daily, along with two anti-

bacterial agents to treat serious pleural effusion [23] but the patient died of acute respiratory failure on the sixth day after hospital admission. Due to the severe nature of the patient's condition and the bacterial complications involved, it would be unwise to imply from this study that ketoconazole is not suitable for treatment of *S. cerevisiae* infection. A number of cases cited in the literature support ketoconazole usage against *S. cerevisiae* and indicate cure of patients infected with *S. cerevisiae* located in the urine and the peritoneum [17]. The eradication of *S. cerevisiae* from the urinary tract was unusual, because ketoconazole is not excreted in the active form. Ketoconazole has been used successfully in the treatment of *S. cerevisiae* vaginitis [9]. In one example, a regime of 400 mg/day for 14 days followed by 200 mg/day led to remission of acute symptomatic *S. cerevisiae* vulvovaginitis. In another case, ketoconazole combined with boric acid (600 mg/day) led to eradication. A 66-year-old male suffering from pancreatic cancer with *S. cerevisiae* disease died after failing to complete ketoconazole therapy [16]. It would seem that susceptibility of *S. cerevisiae* to ketoconazole is either strain dependent or dependent on the body site in which the yeast is located.

The use of boric acid, particularly as a suppository, led to the eradication of *S. cerevisiae* when used against two isolates obtained from patients with symptomatic vulvovaginitis [9]. In the first case, boric acid at 600 mg/day was used in combination with ketoconazole (400 mg/day), leading to eradication. In the second case, boric acid (600 mg twice daily) was the only therapy employed and led to eradication of *S. cerevisiae*. Boric acid suppositories were used with varying degrees of success: in two cases, mycological cure was reported with symptom improvement for one individual, but symptom persistence for the second, and a third case resulted in mycological and symptom remission [12].

Two other azoles should receive mention. Two doses of tioconazole resulted in symptom relief of a 48-year-old woman presenting with vaginitis [12]. The second triazole, voriconazole (UK-109,496), has been tested in vitro against *S. cerevisiae* [42] and had an in vitro minimal inhibitory concentration$_{50}$ (MIC$_{50}$) value of 0.12 μg/ml compared to fluconazole MIC$_{50}$ value of 2 μg/ml. There are no reports of its use against *S. cerevisiae* infection in the clinical literature.

The use of combination therapy is recommended for the eradication of *S. cerevisiae*-induced disease [43] as is prolonged therapy [9]. In conclusion, amphotericin B should be considered the treatment of choice for serious *S. cerevisiae* infection [17,42] except where underlying conditions preclude its use. In cases where amphotericin B therapy is not advised, prolonged treatment with either clotrimazole suppositories, boric acid suppositories, or oral ketoconazole is advised [9]. The use of liposomal forms of amphotericin B should also be considered, especially in cases where infection is severe and triazole therapy has failed.

7. Drug resistance in pathogenic *S. cerevisiae* isolates

A range of antifungal agents have been used to treat *S. cerevisiae* infections and, in many cases, therapy has been unsuccessful. Underlying disease is possibly a factor preventing successful therapy [23]. The worldwide spread of HIV infection has brought about a large population of individuals susceptible to a wide variety of organisms, many of which had previously been regarded as nonpathogenic [44]. During the late 1980s and early 1990s, it was noted that many emerging fungal pathogens such as *Fusarium* and *Trichosporon* species [44] and *Candida krusei* [45] showed inherent resistance to certain antifungals.

The resistance of *S. cerevisiae* to antifungals has been cited in a number of cases [9,17,43]. Fluconazole has been regarded as the treatment of choice for *C. albicans* infections for many years, although AIDS-associated oropharyngeal isolates now show increasing signs of resistance [46]. *S. cerevisiae* has been noted for its resistance to certain drugs, notably fluconazole [9]. In an antifungal susceptibility study, fluconazole resistance in urinary tract *S. cerevisiae* infection was noted [43]. A high MIC value for fluconazole (2 μg/ml) against *S. cerevisiae* compared to both amphotericin B and flucytosine was observed. A study by Espinel–Ingroff [42] also noted an MIC$_{50}$ value of 2 μg/ml for *S. cerevisiae* compared to MIC$_{50}$ of 0.5 μg/ml for *C. albicans*. The inherent resistance to fluconazole highlights the importance of the correct identification of the yeast species in clinical cases in order to provide appropriate therapy.

The *S. cerevisiae* genome contains genes designated as multidrug resistance genes [47]. It has been established that dominant mutations in the Cys$_6$ zinc finger transcription factors PDR1 and PDR3 brings about an increased resistance to a number of agents [47]. These factors are responsible for the activation of an adenosine 5′-triphosphate binding cassette transporter protein-encoding gene PDR5. Transcription of this gene product is required for cycloheximide resistance. The PDR1 and PDR3 gene products also positively regulate YOR1 resistance. YOR1 is an oligomycin-resistance gene whose promoter region contains a PDRE (PDR1/PDR3 response element) 215 bp upstream of the transcription start site. The PDRE site is one of two positive regulators of this gene. Another positive regulatory site and a negative regulatory site also exist but are acted upon by, as yet, unidentified factors [47]. The PDR5 gene contains an identical PDRE sequence to that found in YOR1 and also acts as a positive regulator for transcription. The PDRE found in YOR1 must be fully functional in order for oligomycin tolerance to be conferred on the yeast.

The mechanism of fluconazole tolerance/resistance employed by *S. cerevisiae* is poorly characterized, but it is possible that there are other undiscovered multidrug resistance genes. One way to analyze the likely mechanisms involved is to look at a yeast in which fluconazole resistance mechanisms have been well documented. One such yeast is

C. krusei. The advent of HIV infection and widespread use of triazole antifungals have contributed to the increase in *C. krusei* infections [45]. This is due to the high inherent level of resistance to triazoles found in *C. krusei* [37,44,45]. There are three general methods of resistance found in *Candida* species. First, fluconazole targets the enzyme 14α-demethylase. Alteration of this enzyme stops the build-up of C_{14}-methylated sterols, therefore removing the possibility of membrane disruption. The second method is by decreased uptake of the drug or increased efflux, and third, a deficiency in $C_{5(6)}$ desaturase leading to production of 14-methylfecosterol, which does not affect yeast viability, when 14α-demethylase is inhibited. One study determined that the predominant sterol in *C. krusei* is ergosterol and that fluconazole inhibits 14α-demethylase [37]. It was established that *C. krusei* fluconazole resistance was mediated by reduced susceptibility of 14α-demethylase. It remains unclear which of these resistance mechanisms apply in *S. cerevisiae*. Until further studies are conducted, fluconazole resistance will remain a problem, as will therapy for *S. cerevisiae* disease in general.

8. Implications for biotechnology

Although classically considered to be nonpathogenic, *S. cerevisiae* is now emerging as a cause of disease in immunocompromised patients [7–9]. A number of the virulence factors associated with clinical isolates of this yeast have been identified and partly characterized. It is generally agreed that the factors already described are only part of the overall complement of such factors, and the role of these in the pathogenicity of this yeast is poorly understood [26]. The work cited here indicates that differentiation of yeasts into rigidly defined classes of pathogen and nonpathogen is incorrect. It would appear that a continuum exists between these two categories, and that to consider a yeast such as *S. cerevisiae* as always nonpathogenic is invalid. Although it may not be as virulent as *C. albicans*, some isolates are capable of causing disease and persisting in the host for prolonged periods, particularly in cases of immunocompromization, long-term hospitalization, or prolonged broad-spectrum antibiotic use.

With the identification of the pathogenic potential of *S. cerevisiae*, certain circumstances may preclude the use of this yeast, particularly where immunocompromised individuals may be exposed for prolonged periods. There is ample evidence to suggest that infection by *S. cerevisiae* may result from ingestion of yeast tablets [23,24], from baking [13], or from associating with individuals who work in close contact with the yeast [12]. Caution needs to be exercised by those working in the industrial and biotechnological sectors to ensure that *S. cerevisiae* is treated as a potential pathogen. Consumers and those in the medical profession should also be alerted to the dangers of immunocompromised individuals ingesting brewer's yeast tablets as part of health diets [10,18,24].

It is conceivable that potentially pathogenic isolates of *S. cerevisiae* are currently in use in industrial or biotechnological processes. The ability to distinguish pathogenic from nonpathogenic strains would be of great benefit to commercial users of *S. cerevisiae*, and a number of simple tests may be employed to assist this process. The ability to grow at 42°C is considered to be a crucial characteristic of pathogenic isolates of *S. cerevisiae* [28]. Many clinical isolates are capable of pseudohyphal growth, of producing proteinase, and are capable of phenotypic switching [32]. Many industrially important strains of *S. cerevisiae* are also capable of growth at elevated temperatures (e.g. 40°C) and of producing pseudohyphae [48], so it is conceivable that such strains, if introduced into a suitably immunocompromised host, could result in disease.

While the identification of possible pathogenic isolates may be accomplished in the laboratory, definitive proof of a strain's pathogenic potential would require in vivo testing.

9. Conclusion

Although widely used for the production of bread and alcoholic beverages for thousands of years, *S. cerevisiae* is now being identified as an opportunistic pathogen in a number of cases. Those most at risk appear to be immunocompromised individuals but also patients showing no obvious predisposing factor and those working with the yeast on a regular basis. Although those isolates that have been implicated in disease have a number of clearly defined virulence characteristics, there remains the possibility that yeasts used industrially may have some or all of these factors and so could pose a potential risk to susceptible hosts. In light of the recognition of the pathogenicity of *S. cerevisiae*, industrialists and biotechnologists would be wise to exercise caution when dealing with this yeast, and ensure that it is treated as a potential pathogen rather than as a nonpathogenic yeast.

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