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Growing role of candida albicans as an important cause of nosocomial infection

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Abstract
Candida albicans is an important opportunistic fungus that causes disease in humans as well as in animals. Globally, bloodstream infections due to *Candida* spp. are responsible for 400,000 cases each year. Approximately, 25,000 cases of candidemia occur in the USA annually. Around 90% of AIDS patients suffer from *Candida* infections. *Candida albicans* can colonize practically every human tissue and organ, producing catastrophic infections, despite being a normal microbiota of the humans and animals. It is the most common cause of nosocomial infection in hospitals around the world. A vast range of virulence factors contribute to the ability of *C. albicans* to infect a wide range of host niches. Virulence factors include the expressions of adhesins and invasins on the cell surface, polymorphism, the creation of biofilms, the production of hydrolytic enzymes, and phenotypic switching, among others. The clinical spectrum of candidiasis is wide as it can cause stomatitis, esophagitis, gastritis, vaginitis, balanitis, diaper dermatitis, otitis, endophthalmitis, endocarditis, cystitis, osteoarthritis, candidemia**,** and meningitis. *Candida albicans* with hematologic malignancy and disseminated infection is associated with high fatality rate. Direct microscopy, culture, and biochemical identification are all common phenotype-based *C. albicans* detection approaches. Several molecular biological approaches, including as polymerase chain reaction (PCR), real-time PCR (RT-PCR), mass spectrometry, and immunoassay, have also been used to detect *C. albicans.* Patients infected with *C.albicans* are treated with a variety of antifungal medicines, including clotrimazole, miconazole for topical treatment, and fluconazole and itraconazole for systemic injection. Keeping the skin clean and dry, adjusting food preferences, avoiding frequent use of antibacterial soaps, taking medications as advised by a doctor, and maintaining a healthy lifestyle are the best preventative actions that can be taken. In immunocompromised patients, early diagnosis and prompt chemotherapy are essential to avoid complications. The typing of *C.albicans* by restriction mapping is imperative to investigate the spread of the pathogen in hospital wards.

Keywords: *Candida albicans*, diagnosis, immunocompromised host, nosocomial infection, treatment

Introduction
Currently, fungi are becoming more widely recognized as significant cause of morbidity as well as mortality, especially in immunocompromised patients (Pal, 2017) [40]. *Candida albicans* is the chief etiological agent of candidiasis, which is reported from many countries of the world including India, Brazil, Italy, and USA (Pal, 1987; Pal and Desai, 1998; Moreira and Paula, 2006; Milazzo *et al.*, 2014; Mehta *et al.*, 2018; Ricotta *et al.*, 2021) [42, 28, 5, 35, 26, 50]. *Candida* species, with *Candida albicans* being the most common species, have become the fourth most common cause of nosocomial bloodstream infections in immunocompromised patients (Apaire-Marchais *et al.*, 2008; Milazzo *et al.*, 2014; Ricotta *et al.*, 2021) [1, 26, 50]. Many non-albicans species, such as *C. glabrata, C. parapsilosis*, and *C. tropicalis*, have recently emerged as important pathogens in debilitated individuals (Junqueira *et al.*, 2011; Pal *et al.*, 2015; Ricotta *et al.*, 2021) [19, 50, 43], with *C. parapsilosis* being the second most common fungal species isolated from the blood in many parts of the world (Moran *et al.*, 2002; Yang *et al.*, 2021) [59, 27].
Candida albicans is a common opportunistic pathogen that lives in the nasopharynx, gastrointestinal tract, and external genitalia. In humans, it colonizes as a commensal in 30-50% of healthy people (Davidson *et al.*, 2018) [6]. Patients with a weakened immune system, on the other hand, are more likely to develop systemic infections caused by *Candida* species. *Candida albicans* is a common cause of infections, such as denture stomatitis, thrush, and urinary tract infections in humans, but it can also cause more serious systemic diseases. The fungus often causes life-threatening infections, especially in immunocompromised people (Pal, 2020; d'Enfert *et al.*, 2021) [7, 42].

Mortality rates associated with invasive candidiasis can range from 37 to 70% (Pappas *et al.*, 2018; Koehler *et al.* 2019; Mahalingam *et al.*, 2022) [48, 20, 23]. It is important to mention that the current incidence of candidaemia in Europe is 79 cases per day, of which about 29 patients have serious outcome at day 30 (Koehler *et al.* 2019) [20].

Candida albicans is most commonly seen in birds, where it affects the oral mucosa, esophagus, and crop. Pigs and foals have been reported to suffer superficial infections restricted to the mucous membranes of the intestinal tract. Cattle, calves, lambs, and foals have also developed systemic candidiasis as a result of prolonged antibiotic or corticosteroid therapy. *Candida* infection is uncommon in cats; however, it has been linked to oral and upper respiratory infections, pyothorax, ophthalmic lesions, intestinal illness, and urocystitis. The infections in dogs and horses are uncommon. *Candida* spp., on the other hand, it has been linked to arthritis in horses, as well as mastitis and abortion in cattle (Toboada, 2018) [57]. Recently, Pal (2015) [43] has elucidated the etiologic role of *Candida albicans* in mastitis of camel for the first time from Ethiopia. The objective of this mini review is to delineate the growing significance of *Candida albicans* as a major cause of nosocomial infection in humans. In addition, the efficacy of Pal sunflower medium for the isolation of *Candida albicans* and other species from various types of clinical samples from humans and animals is also discussed.

Morphology and characteristics

Candida albicans an opportunistic fungus that belongs to the family *Candidaceae*, is a polymorphic fungus that can take the form of yeast or pseudohyphal depending on the temperature, pH, and nutrients. The yeast form with blastoconidia budding is the most prevalent, and pseudohyphae forms lack the right structural forms of real hyphae, which are sprout-like and can grow thick walled chlamydospores, such as parallel walls and septation. Budding happens during asexual reproduction, resulting in the creation of blastoconidia (Ingle *et al.* 2017) [17].

On corn meal agar, two morphological forms of *Candida albicans* are visible: chlamydospores found individually or in clusters, and blastoconidia developed in dense clusters at septations with branched and true hyphae (ICMR, 2019) [16].

Host spectrum

Natural *Candida* infections have been frequently described in humans and also in a wide variety of animals (Pal, 1987; Pal and Desai, 1998; Pal, 2007) [35, 38, 42]. The animals affected from *Candida* infections include baboon, bear, beaver, budgerigar, buffalo, camel, cat, cattle, chicken, crane, dog, dolphin, duck, emu, ferret, finch, fish goat, gorilla, goose, guinea fowl, guinea pig, horse, lion, lorikeet, monkey, mouse, parrot, partridge, peacock, pleasant, pig, pigeon, quail, rabbit, sheep, squirrel, tortoise, turkey and whale (Pal,1980, Pal and Matsusaka, 1994; 1994; Pal and Lee,1999; Pal and Rao, 1999; Pal, 2002; Pal, 2007; Pal,2015) [44, 34, 43, 45, 46, 37, 38].

Transmission

The modes of transmission and entry sites for fungal infections differ depending on the pathogen. *Candida* infections are mostly caused by endogenous sources, but cross-infection through the hands of health-care providers or family, as well as by gadgets, has been documented (Muňoz *et al.*, 2001; Sakita *et al.*, 2017) [30, 53]. *Candida albicans* is frequently transmitted from mother to child during childbirth and becomes part of a healthy person's microbiota (Pal, 2007; d'Enfert *et al.*, 2021) [38, 7]. The infection due to *C.albicans* can be sexually transmitted to male partner causing balanitis (Pal, 2007) [38]. The usual reservoir of *C.albicans* is found in the normal human microbiota. In hospital settings, where immunocompromised patients acquire the yeast from healthcare workers, people-to-people infections are most common (Fanello *et al.*, 2001) [8]. *Candida* infections may also develop following renal transplantation, cauterization, dialysis, and other surgical interventions (Pal, 2007) [38].

Virulence factors and pathogenesis

Candida albicans is found on the skin and mucosal surfaces of 80% of healthy people's genital, intestinal, vaginal, urinary, and oral tracts. An immune mismatch between the host and this opportunistic fungus may result in mucosal infections, followed by bloodstream spread and infection of the internal organs (Henriques and Silva, 2021) [14]. *Candida albicans* is the most prevalent opportunistic pathogenic fungus in humans, accounting for 60% of mucosal infections, and 40% of candidemia cases (Goncalves *et al.*, 2016; Pappas *et al.*, 2018) [48].

Candida albicans infections are caused by a number of virulence factors, including adhesion to the host and abiotic medical surfaces, biofilm formation, and the production of hydrolytic enzymes (Henriques and Silva, 2021) [14]. Their ability to colonize host tissues, cause disease, and overcome host defenses is aided by virulence factors (Sabino *et al.*, 2011) [51]. *Candida* has ability to adapt to a range of habitats, and the production of surface-attached microbial communities known as biofilms, is one of its virulence factors (Junqueira *et al.*, 2011) [19]. *Candida* biofilms can form on natural host surfaces as well as biomaterials utilized in medical devices like silicone and dental prosthetics like acrylic resin (Silva *et al.*, 2010, Noumi *et al.*, 2010; Bajunaid, 2022) [54, 33, 2]. *In vitro* biofilm formation is divided into three stages: (i) yeast cell attachment and colonization, (ii) yeast cell growth and proliferation to allow the formation of a basal layer of anchoring cells, and (iii) growth of pseudohyphae and extensive hyphae concurrent with the production of extracellular matrix material (Junqueira *et al.*, 2011) [19]. *Candida* biofilms act as a long-term reservoir of infection and are more resistant to antifungal treatments once developed (Silva *et al.*, 2010) [54]. Other virulence factors include the ability to secrete hydrolytic enzymes such as aspartic proteinases and lipases (Sabino *et al.*, 2011) [51], as well as the ability to grow in a variety of morphological forms, ranging from unicellular budding yeast (blastospores), pseudohyphae, and true hyphae with parallel-sided walls (Ferreira *et al.*, 2010) [9]. The yeast-hyphae transition is an essential virulence factors that leads to tissue penetration and escape from phagocyte cells after host internalization (Kumamoto and Vinces, 2005) [21].

Clinical spectrum

Candida species produce a wide array of clinical symptoms, such as diaper dermatitis paronychia, onychomycosis, cheilitis, glossitis, laryngitis, stomatits, esophagitis, gastritis, vulvovagintis, balanitis, pericarditis, endocarditis, pneumonia, peritonitis, pancreaitis, cystitis, arthritis,

osteoarthritis, pneumonia, endophthalmitis, otitis, meningitis, septicemia, and others (Jadhav *et al.*, 2003; Moreira and Paula, 2006; Pal,2007; Sobel,2007; Chander, 2009; Pal, 2020; Moreira *et al.*, 2021) [18, 38, 29, 42, 55]. *Candida albicans* has the potential to cause infections in immune-compromised as well as in healthy individuals (Pal and Desai, 1998; Pal, 2007; Pal, 2020) [42, 38]. It is reported that about 50 to 70% of women in child bearing age may experience at least one episode of vulvovaginal candididasis each year (Sobel, 2007) [55]. *Candida albicans* remains the main cause of vulvovaginitis in women worldwide (Pal, 2007; Moreira *et al.*, 2021) [29, 38]. Oropharyngeal candidiasis due to *Candida albicans* is frequently observed in AIDS patients (Fig.1).

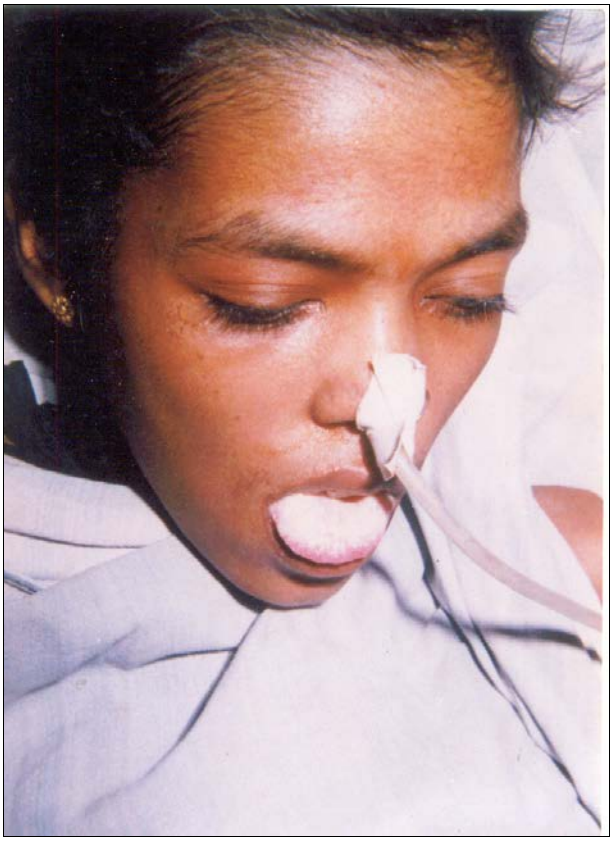

Fig 1: A severe form of oropharyngeal candidiasis due to *Candida albicans* in a young woman with concurrent infection of AIDS and tuberculosis.

Source: Pal (2007) [38]

Diagnosis

The yeast can be easily isolated from the clinical specimens of the patient on mycological media, such as Sabouraud dextrose agar (Pal and Desai, 2004) and Pal sunflower seed medium (Pal, 2007) [38]. The later medium, which contained 45 g of pulverized sunflower seed, 20 g agar, 500 mg chloramphenicol, and 1000 ml of distilled water was developed by Pal in 1980 [34] for the rapid isolation and identification of *Cryptococcus neoformans* from clinical and environmental specimens (Pal, 1997) [36]. On Pal sunflower seed medium, *C. neoformans* produces light to dark brown pigmented colonies whereas *C. albicans* shows cream colored, pasty and smooth colonies (Fig. 2). The efficacy of Pal sunflower seed medium for the isolation of *C. albicans* from different types of clinical samples, such as scrapings from oral ulcers in a healthy subject (Pal and Desai, 1998) [42], pneumonic lung tissue of goat (Pal and Lee, 1999) [46], ear debris from the otitis cases in humans (Jadhave *et al.*, 2003) [18], oropharyngeal swab from an AIDS patient (Pal, 2007) [38] and mastitic milk in a camel (Pal, 2015) [43] have been studied extensively. It is interesting to state that Pal sunflower seed medium also supported the growth of other species of *Candida*, such as *C. guilliermondii*, *C. parapsilosis* and C. *tropicalis* (Pal, 2007) [38]. It is important to mention that candidemia is identified mostly through blood cultures; however, when antibiotics fail, it often becomes the evident infection (Mikulska *et al.*, 2012) [25].

Source: **(**Pal, 2007) [38].

Fig 2: Many smooth, pasty, cream colored colonies of *Candida* spp. grew on Pal sunflower seed medium at 25 ^{0}C after 8th days of incubation. The yeast was isolated from the clinical specimen of a compromised patient. The brown pigmented colonies are of *Cryptococcus neoformans*.

Traditional diagnostic techniques in humans, such as blood cultures and biochemical assays, lack the sensitivity and specificity needed to ensure accurate and timely detection of invasive *Candida* infections (Stevens, 2002, White *et al.*, 2003) [56]. As a result, technologies based on yeast DNA amplification and detection has been developed (Zhao *et al.*, 2019) [60]. For the specific and rapid detection and identification of fungi from clinical isolates, traditional polymerase chain reaction (PCR) techniques and now real-time PCR assays are used (Hsu *et al.*, 2003; Busser *et al.*, 2020) [15, 4]. Magnetic beads coated with monoclonal antibodies are used to collect yeast cells present in clinical specimens in the immuno magnetic separation method (IMS). IMS is one of the most sensitive technologies for detecting tiny quantities of DNA from pathogens in clinical samples, and it could be useful in diagnosing candidemia (Apaire-Marchais *et al.*, 2008) [1].The routine application of Pal sunflower seed medium for the isolation of *C. albicans* from clinical samples is advised.

Treatment and prevention

Fluconazole is the most common treatment for candidiasis in healthy persons: 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily. Echinocandin (caspofungin, micafungin, or anidulafungin) or amphotericin B is preferable for neutropenic patients (Pappas *et al.*, 2016) [47]. Patients with candidemia are commonly given fluconazole intravenousor oral, but echinocandin and lipid-formulated

amphotericin B are preferable in severely ill patients. Despite this, fluconazole medication had the fewest negative effects (Nguyen *et al.*, 1995) [32]. Oral yeast isolates from Tanzania demonstrated significant susceptibility to fluconazole, itraconazole, miconazole, clotrimazole, and amphotericin B, as well as reduced susceptibility to fluconazole, itraconazole, miconazole, and clotrimazole in the treatment of candidiasis (Hamza *et al.*, 2008) [13]. Oral ulcers due to *C. albicans* in an immunocompetent patient were successfully treated with 1% solution of clotrimazole solution and ketoconazole at the dosage rate of 200 mg orally for 10 days without any side effects (Pal and Desai, 1998) [42].

The prevention and treatment of candidiasis are mostly dependent on two crucial and critical aspects. One is the detection and identification of *Candida* strains at an early stage. The second step is to take antifungal medications that are effective (Nguyen *et al.*, 1995) [32]. Recent research has also observed a higher prevalence of *Candida albicans* in obese individuals (Barber *et al.*, 2020; García-Gamboa *et al.*, 2021) [3, 11]. A healthy lifestyle, including good hygiene, well-balanced nutrition with plenty of fiber and sugar reduction, consumption of probiotics and flavonoid-rich foods (e.g. tea, onions, berries, apples, tomatoes, kale, red peppers), antibiotic stewardship, cotton underwear and loose pants, and changing wet garments is imperative (Sagar, 2018; Kumamoto *et al.*, 2020; Gao *et al.*, 2021; d 'Enfert *et al.*, 2021; Ribeiro *et al.*, 2020; Nguyen *et al.*, 2021) [52, 31, 10, 22, 49]. It is pertinent to mention that predisposing factors, which favors for the development of *Candida* infections must be avoided (Pal, 2007) [38].

Conclusion

Candida albicans plays a significant role in nosocomial infections. Many *Candida* species have lately emerged as major infections in immunocompromised patients, with *C. albicans* being the most important. *Candida albicans* is an important globally prevalent opportunistic pathogen that can be found in the nasopharynx, gastrointestinal system, and external genitalia. It causes wide variety of clinical symptoms, such as stomatitis, vulvovaginitis, cystitis, and others in healthy and compromised individuals. *Candida* infections are mostly caused by endogenous sources, and clinical infections have been reported in humans as well as in many species of animals including poultry. Most pathogenic *Candida* species have evolved a wide range of putative virulence characteristics, including the ability to form biofilms, secrete hydrolytic enzymes, and proliferate in a variety of morphological shapes. The prevention of *Candida* infections and maintaining a healthy lifestyle are the best preventative action that can be taken for those affected. It is emphasized to conduct additional studies on the virulence, pathogenesis, molecular epidemiology, and predisposing factors in immuno compromised and immuno copetent subjects. The wider application of Pal sunflower seed medium due to its low cost is recommended in the microbiology and public health diagnostic laboratories for the isolation of yeast from various types of clinical specimens. The systematic detailed research work on the growing role of non- *albicans Candida* (NAC) species in the etiology of some other clinical disorders of humans as well as animals may be rewarding.

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Ethics approval and consent to participate

This manuscript is a review article and does not need Ethical approval. Further, it has no questionnaire survey.

Consent for publication

The authors have agreement for this review for its publication.

Availability of data and material

All the data and materials are present on hands of each author.

Competing interests

The authors declare that there was conflict of interest.

Authors' contributions

All the authors contributed equally. They read the final version, and approved it for the submission to the journal for publication.

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