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A REVIEW OF THE PREVALENCE AND ANTI-FUNGAL RESISTANCE PROFILE OF *CANDIDA*CAUSING CANDIDURIA IN PATIENTS WITH DIABETES

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Background: It is estimated that around from 10-30% of people with diabetes also have a major case of candiduria in globally. According to 2019 predictions, there are 37 million people in India who are expected to have prediabetes and around 73 million people who have diabetes. Diabetes is the main risk factor for candiduria, this vulnerabel disease may lead to lower the immunity of an individule. Patients with low immunity favaour the *Candida* to cause infections and also responsible for resistant of anti-fungal drugs. Therefore, Candiduria in DM patients have higher mortality rate. The purpose of this review is to figure out the overall incidence and resistance pattern of *Candida* in patients with diabetes mellitus.

Objectives: This study's objectives included a review of the incidence of candiduria in people with diabetes mellitus and the distribution of antifungal resistance, and the identification of candiduria risk factors.

Methodology: Multiple search engines (PubMed, EMBASE, MEDLINE, and Google scholar) were used to conduct a thorough English language literature search. A total of 200 articles were extracted and 149 of them were selected for the study.

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Results:*Candida albicans* (≥ 30%) was more prevalent followed by *Candida glabrata*(≥ 10%). Fluconazole was exclusively effective against *C. tropicalis*, while the other half of the *C. albicans* species were all susceptible to it.

Conclusion: Identifying the species of *Candida* correctly is crucial in these complicated situations to choose the most effective antifungal therapy.Therefore, to aid physicians in providing patients with candiduria with better care, it is important to regularly identify the species of *Candida* and their pattern of susceptibility to antifungals.

Keywords: Candiduria, *Candida albicans*, N*on-Candida albicans*, Diabetes mellitus, Antifungal, Fluconazole.

Introduction:

The urinary tract is often colonized by *Candida* species.The existence of a *Candida*in the urine is referred to as candiduria"[1, 2]. The healthcare professional finds it extremely difficult to determine if the candiduria is a sign of colonisation or an upper or lower urinary tract infection. [3-12]. The important clinical significance of candiduria is highlighted by the substantial risk of morbidity and mortality linked to this illness in people with immunocompromised conditions [13]. It is estimated that around from 10-30% of people with diabetes also have a major case of candiduria in globally [14]. Hyperglycemia is a hallmark of chronic metabolic diabetes mellitus (DM). In the twenty-first century, it is growing to be one of the newest hazards to public health [15,16,17]. The serum concentration of glucose is higher in diabetics than in healthy people [18]. In 2017, about 425 million people worldwide had adult-onset of diabetes (20–79 years old).The International Diabetes Federation and the WHO projected that by 2045; there will be close to 629 million adults worldwide who had diabetes [19-24]. Many studies have been conducted on the association between candidiasis and diabetes, especially because people with diabetes are more likely than those without the disease to get fungal infections [24-29].Low immunity makes the gastrointestinal and urinary tracts, as well as the mucosal membranes, more vulnerable to infectious pathogens in individuals with elevated levels of glucose in their blood and diabetes that is uncontrolled. [30]. Approximately 10–30% of patients experiences with candiduria indicate that of*Candida* species exists in the urinary bladder. In addition to DM patients, hospitalized patients, particularly those in critical care facilities (ICUs) and intensive care units for newborns (NICUs), frequently develop candiduria[31].According to 2019 predictions, there are 37 million people in India who are expected to have prediabetes and around 73 million people who have diabetes [32]. Diabetes is the main risk factor for candiduria and responsible for resistant to many antifungal drugs. *Candida*infections in humans aredeveloped by adhesionand invasion to epithelial cell [33].These virulence factors significantly affect the equilibrium between the host and yeasts, encouraging *Candida spps* transformation from normal flora to pathogen and resulting in infection [34]. Epidemiology investigations have shown that patients with candiduria most frequently isolate the species *Candida albicans*and followed by Non-*Candida albicans* (NCA) [35]. When 90% of AIDS patients with DM and Co-morbid were found to have candiduria and many of them had undergone long-term azole medication, azole-resistant

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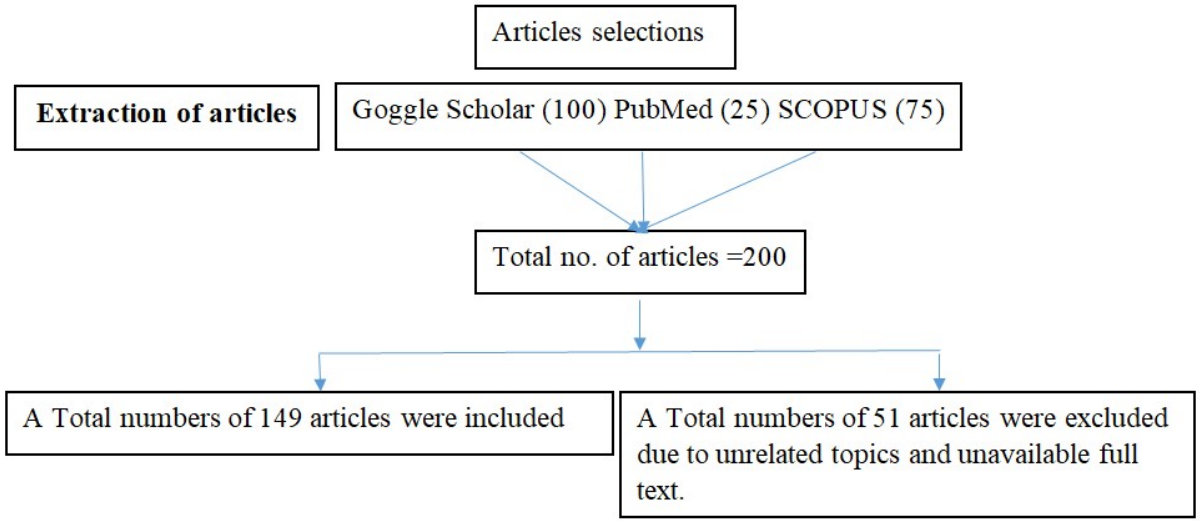
*C. albicans*and NCAbecame a serious concern [36].Nosocomial infections that cause candiduria in diabetic patients include *Candida glabrata* and other NAC species,notwithstanding the *C. albicans*is the primary causes of candiduria and lead to antifungal resistance. However, due to rising antifungal treatment resistance, Non *Candida albicans* species have also been connected in recent years [37]. The urine of a diabetic patient with candiduria has been shown to contain *C. auris*, a newly discovered multidrug-resistant *Candida* species [38].The routine identification of various *Candidaspp*. in clinical microbiology laboratories has evolved over recent years, making it possible to detect more and more species of NAC. The most common class of drug used to treat candiduria is azoles compounds, which is not effective against some species of NCA.The objective of this review was to give an update on prevalence of candiduria and resistance pattern Candida identified from DM patients with candiduria.

Strategies for searching and choosing articles:

MeSH terms such as UTI, funguria, candiduria, and candiduria were the search phrases used. All full-text English publications have been chosen for evaluation, and appropriate data has been extracted. PubMed, Scopus, and Google Scholar searches were performed on published works.The Medline database via PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/home.uri), Google Scholar (https://scholar.google.com/), and Google were the worldwide sources utilized to search the literature.A total of 200 articles were extracted from these web site and 149 of them were selected for the study.



Prevalence:

Candida infection has reached epidemic proportions worldwide, particularly in underdeveloped countries such as India. The prevalence of candiduria in hospitals is growing with 10% to 15% of the cases. Abhishek VC*et al.,* in 2019 from India, 50% of the population falls into the age range of 21 to 30 years old. Cases of candiduria account for 92% of non-ICU cases. Ninety-two percent of patients who are not diabetic have candiduria [39]. Mishra N *et al.,* in 2022 were identified the

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incidence of Candida species was 11.2% in Uttar Pradesh [40]. Oladugba EO et al in 2022 studied the prevalence of candiduria is 54.55% in Nigeria [41].Gharaghani M*et al.,* in 2018 analyzed the average occurrence was almost 16.5%. in Iran *[42]*.Elsaeed AM *et al.,* in 2020 was discovered that candiduria were more DM patients (79%) than the patients without DM (41%) in Egypt [43].Talapko J *et al.,* in 2022 reported that those with type II DM, the prevalence of candiduria varies from 2.27% to 30%. [44]. In 2016, Balakumar P *et al*. conducted research indicating that a total of 422 million people globally are affected by DM, with the mainstreamexisting in modest income nation. The WHO estimates that the disease is directly accountable for 1.5 million deaths every year [45, 46]. Thakur JS *et al.,* in 2022 conducted in Punjab, the prevalence of diabetes was 14.3%, whereas in Haryana, it was 15.1% [47]. Vaz NC *et al.,* in 2011 showed in rural Meerut, the prevalence of diabetes in those 30 years of age and above was reported to be 11.7% in North India [48]. Fraisse T *et al.,* in 2011 claimed in France, 8.9% of extremely old patients in hospitals had candiduria [49].Sumana MN found that total candiduria was present in 58.32% of people in Karnataka in 2023. [50].In 2023, Yadav RK et al. discovered that the occurrencepercentage of candiduria in ICU patients was 3.26% in New Delhi [51]. In 2020, Manikandan M researched type 2 diabetic patients in Chennai and discovered that 25% of them had Candiduria [52].In 2022, Singh AA *et al*. claimed that the frequency of candiduria was 18.1% in Haryana [53].Pawar M et al. (2015) conducted study on 35.6% "*C. albicans*, 64.4% non-*C. albicans*, and the rest *C. tropicalis* (33.7%), *C. glabrata* (17.3%), and *C. parapsilosis* (5.8%)". The most isolates were from sputum and bodily fluids, followed by pus, tissue, and urine [54].

VIRULENCE FACTORS: WHAT ARE THEY?

The potential of a microorganism to spread through its host and cause infection is known as virulence.In *C. albicans*, host recognition is a component of pathogenicity, just like in other infections. Co-aggregation which occurs when *Candida* bind to host cells and proteins. The promotion of virulence by a number of degradative enzymes has also been demonstrated [55, 56].

Candidaand its virulencefactors

The main cause of fungal nosocomial UTIs and systemic candidiasis globally is the dimorphic fungus *Candida*. The dimorphic fungus *Candida* is known to have several pathogenic features, one of which is morphological flexibility, which allows it to transform from filamentous and yeast or yeast to filamentous forms.Furthermore, a number of traits, including adhesion, invasion, the release of hydrolytic enzymes, stereotropism, and the creation of biofilms, are undoubtedly recognized as pathogenic mechanisms exclusive to *Candida* [57]. The invasion of mucosal surfaces may be facilitated by any of these processes. Finally, it has been suggested that the phenomena of "phenotypic switching" contributes to the organism's flexibility. Along with variations in colony phenotype, there are also variations in adherence characteristics, antigen expression, and tissue affinities. Each of these virulence variables is discussed below.

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Adhesions and invasion

A biomolecule known as an adhesion is one that adherence to host cells. Numerous accounts of *C. albicans* spontaneous mutants that were non-adhesive and virulent served as inspiration for the research of host recognition[57-60]. These investigations undoubtedly played a critical role in helping us comprehend how *Candida albicans*and Non *albican Candida*interacts with its host.Nonetheless, the majority of the next conversation will centre on identifying the genes responsible for encoding a protein that recognises hosts. *Candida* uses a unique class of proteins known as adhesions in both of its life forms—pathogenesis and commensalism—to successfully cling to inanimate surfaces and host cells. Therefore, an intense bond to avoid being washed away is the first and most important component for the pathogenic *Candida*. *Candida's* filamentous form depends on adhesion activity mediated by two sets of protein families: "Als [agglutinin–like sequence (Als1–7 and Als9)] and Hwp1 (Hypha associated GPI–linked protein) adhesions". The Als3 protein is crucial for adhesion among the Als proteins. The als and hwp1 genes, respectively, produce the aforementioned proteins [61-65]. Conversely, pathogenic strains of *Candida* have an innate process in their hyphal structure called invasion. In order to invade host cells, invasions are often mediated by one of two simultaneous invasion mechanisms.Invasions are specific proteins on the surface of hyphal cells that mediate the triggered endocytosis mechanism. The Als3 and Ssa1 proteins are involved in the most significant invasions. The adhesion-invasion protein Als3 is used in the fungal hyphae of *Candida* to promote adherence and invasion. Moreover, the Ssa1 protein belongs to the heat shock protein 70 (HSP70) group, which invades *Candida*hyphal filaments in combination with Als3. Various sources of evidence indicate that stereotropism and biofilm development are significant components of pathogenicity in pathogenic strains of *Candida* [57, 64, 65].

Candidaand its polymorphism (Morphogenesis)

The change from yeast monocellular cells to a filamentous growth form is referred to as morphogenesis. Unicellular yeast cells can change reversibly into either pseudo-hyphal or hyphal development. The fungal colonization and infection strategy is determined by the morphology of *Candida albicans*. The3formsof*Candida* compriseovoidshapebuddingyeast,looseseptatepseudo-hyphae. In corn meal agar *candida* produce terminal chlamydospore as shown in figure 1. "In accordance to that yeast cells and pseudo-hyphaeboth contributed to candiduria and the pseudo hyphal form with budding yeast cellof *Candida* in vivo condition as shown in figure 2".In the context of morphogenesis, there has long been research into connecting virulence to *C. albicans'* filamentous shape [57,66].

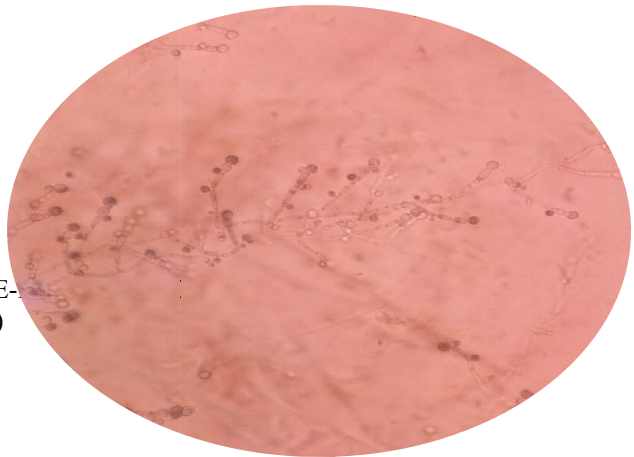

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Fig1:Figure representthat*Candidaalbicans* with terminal chlamydospore (40X).

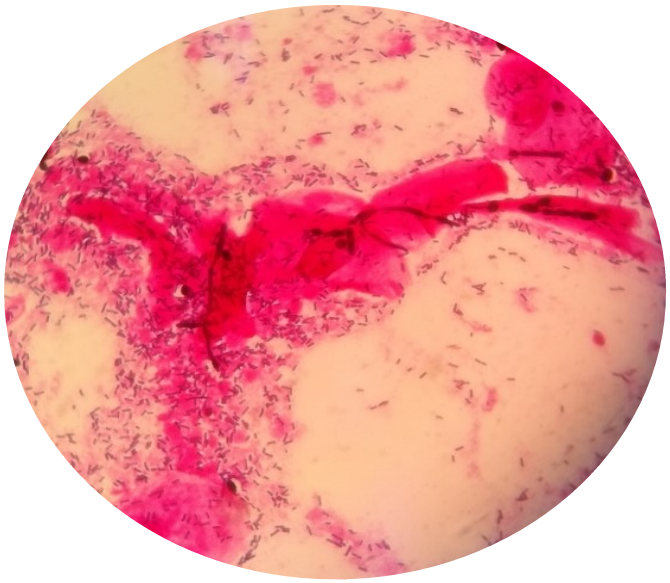

Fig2:Gram staining of high vaginal swabs showing that Yeastand pseudo hyphae of *Candida* species (100X).

Enzymes that contribute to invasiveness

Two important enzymes in *Candida albicans* that are link to virulence, there are secreted aspartyl proteinases (SAP) and phospholipase (PL). The SAP enzyme is coded with 10 SAP (*SAP1 to SAP10*) gene family and responsible for early adherence, penetration, and skin infections, oral and vaginal infections.Phospholipase is a heterogeneous enzyme there are 4 types such as PL-A, PL-B, PL-C and PL-D. During the host cell invasion phospholipses are present on tips of hyphal. Phospholipases are responsible for damage to the cell membrane and penetration of the host cell during invasion. During the host cell invasion phospholipses are present on tips of hyphal[67].

Phenotypic switching

Pomes et al. showed that *C. albicans* colonies became rough at high frequencies in response to mild doses of UV radiation, and that these colonies thereafter reverted to their original smooth phenotype at frequencies [68]. As a result, the colony phenotypic flipping was both reversible and frequent. Star, stippled, hat, irregular wrinkle, and fuzzy colony forms may all be seen, according to S. Lutsky*et al*. utilizing strain 3153A to extend their findings [69]. Additionally, several of these colony types subsequently converted to different phenotypes, demonstrating that

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frequent change between the various phenotypes takes place. Interestingly, although using the identical substrate, strain-specific switch phenotypes were seen.

PATHOGENESIS:

Candida albicans, are a permanent resident of the body of an individual and may lead to a variety of superficial, cutaneous, and systemic infections. While risk factors play a significant role in the development of candidiasis, microorganisms are linked to several pathogenicity factors that facilitate their invasion of host tissues. The pathogenicity of *Candida* is linked to a number of processes, such as the creation of biofilms, extracellular enzymes, germ tube formation, and phenotypic switching [70-78]. Numerous studies have demonstrated the important of hydrolytic enzyme release plays in the pathophysiology of *Candida* species, including lipases, phospholipases, and proteases [77,79]. It has also been shown that adhesion to tissue surfaces, heat shock proteins, galvanotropism, and thigmotropism can all contribute to the ensuing candiduria [75,79]. Furthermore, a few of these elements, such the development of biofilms, may obstruct antifungal treatment [78-80]. On the other hand, frequent use of antifungal prophylaxis may make *Candida* more pathogenic and develop its resistance to these medications [81,82].

RISK FACTORS RELATED TO HOST

Even though species of *Candida* are a typical part of the human mycoflora, candiduria is unusual in healthy persons. Conversely, those who have predisposing conditions and those who are hospitalized tend to have candiduria more frequently [83,84]. An imbalance in the host defense mechanism can result from several factors such as underlying diseases, burns, invasive procedures, and skin maceration, which affect the host defense mechanisms [85,86]. Consequently, commensal microbes infiltrate the tissues of the hosts. Many risk factors are present in patients, including cancer, neutropenia, genitourinary TB, diabetes mellitus, immunosuppressive medication, long-term antibiotic therapy, elderly age, prior surgery, leukemia, chronic kidney disease, kidney transplantation, and bone marrow transplantation [70, 83, 87-92]. Diabetes is a serious metabolic condition associated with sluggish lifestyles and poor eating habits. In the most catastrophic case scenario, metabolic issues are the root cause of many other illnesses. DM is one of the conditions that raises blood sugar levels and influences *Candida* to case infection [149].Due to intrusive therapeutic and diagnostic treatments, Candidaemia can strike up to 21% of hospitalised patients at some point during their stay [93,94]. Patients who get corticosteroid medication or who have hematologic malignancies may also be at risk for developing candiduria [93, 95, 96]. Other risk factors for candiduria include female genders, kidney stones, urinary tract obstruction, and benign prostatic hyperplasia [97-102]. The literature has extensively examined the correlation between the “catheterization and antibiotic therapy” and the rising prevalence of candiduria [87, 96, 103]. Biomaterials such as catheters induce the production of biofilms which is the major virulence factors of *Candida* into the urinary system. According to certain reports, 78% of patients who use urinary devices also have candiduria [87].Conversely, individuals with acquired immunodeficiency syndrome (AIDS) also showed a

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marked rise in the prevalence of candidiasis [104,105].The family of cephalosporin was the most often recommended antimicrobial drug for individuals in whom candiduria was found, according to the Paul *et al.* study [88]. Other research' conclusions indicate that there is a strong correlation between chronic antibiotic use and candiduria [106, 107]. The prevalence rates of candiduria have been reported to increase with urinary catheterization followed by prolonged antibiotic use, abdominal surgeries, diabetes mellitus, and use of corticosteroids and immune suppressants based on the findings of Guler*et al.* [108].

Candiduria:

Candiduria by that arise in hospitals are associated with *Candida* sp. in between 10% and 15% of cases, and the frequency is still rising [109]. Candiduria risk can be raised by certain predisposing circumstances, including diabetes mellitus. Particularly, because of its numerous modifications to the genitourinary system, diabetes mellitus has been linked to extremely complex Candiduria [110]. Since the 1980s, there has been a notable rise in candida infections of the bladder and kidneys. While *C. albicans* is the utmost frequently isolated species and NAC species is currently prevalent in many places across the world [111,112]. Hospitalized patients are more likely to have candiduria, or the presence of *Candida* sp. in their urine [113], and those who have diabetes mellitus are more susceptible to Candiduria. Consequently, lowering risk factors like lowering blood sugar levels and getting rid of urinary catheters can cause candiduria to go away [29]. DM and *Candida* species-related physiopathology and aetiology linked to candiduria incidence, respectively and also found that candiduria was significantly correlated with women because of short urethra, increased blood and urine glucose, uncontrolled diabetes [114]. Most common *Candida* species are responsible for candiduria is*Candida albicans* followed by NAC species [114]. Several risk factors, including being overweight, having hypertension, and abnormalities in the metabolism of sugars, come together to form metabolic syndrome, which raises blood glucose levels and eventually causes diabetes mellitus [148].Esmailzadeh*et al.* [112] assessed candiduria in patients with type II DM. In fact, the findings demonstrated that patients with type II DMhad a comparatively high risk of candiduria in addition to inadequate blood glucose management. Even though NAC species was more common than *C. albicans*, they were more prevalent in individuals who had symptomatic candiduria [112].Candiduria is more common in symptomatic and asymptomatic DM patients as well as related risk factors [109]. Patients with type IIDM who were asymptomatic or symptomatic, significant candiduria were found in 7.5% and 17.1% of cases, respectively. Of the isolated *Candida* sp., 84.2% were found in diabetic patients who did not exhibit any symptoms, and the remaining 15.8% were found in individuals. In their research, Rizzi and Trevisan examined the influence of SGLT-2 inhibitors on the occurrence and severity of UTI problems in people with diabetes. The investigators came to the conclusion that the only people linked to poor glycemic control [115]. The use of antibacterial drugs, sex (female), diabetes mellitus, and indwelling bladder catheters have been determined to be risk factors for both *Candida albicans* and *Candida glabrata* candiduria [111], as previously described [116-119]. This illness is linked to a gas formation that might exhibit as pyelitis, pyelonephritis, or cystitis. Uncontrolled diabetes

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mellitus creates a conducive environment for the growth of gas-forming organisms, which makes it a significant risk factor for this kind of illness [120,121]. A patient with uncontrolled diabetes mellitus was diagnosed with pyelitis by *C. tropicalis* in a case described by Alansari*et al*. [122], while a 53-year-old age patient had emphysematous cystitis which was produced by *C. tropicalis* in a case published by Wang *et al.* [123, 124]. The use of broad-spectrum antibiotics and diabetes mellitus were the risk factors. Severe UTIs such as pyelonephritis and emphysematous pyelonephritis were more frequently linked to uncontrolled diabetes.Urinary catheterization and diabetes mellitus have been directly linked to bloodstream infections caused by biofilm-forming *Candida* sp., according to research by Tumbarello*et al.* [126]. The injured bladder and the urethral mucosa allowed *Candida albicans* to eventually spread into the bloodstream. Additionally, those isolates developed voriconazole resistance and continuously produced high amounts of biofilm formation in vitro [65]. Suzuki *et al*. [125] investigated into the connection between glucosuria and UTIs in an additional research study. They observed how SGLT2 inhibitor-induced glucosuria affected the development of UTIs in mice. Based on the findings, mice given dapagliflozin and canagliflozin (but not tofogliflozin) had higher kidney concentrations of *C. albicans* in relation to treatment time and dosage [126].

Antifungal Resistance pattern:

Treatments for fungal infections affect *Candida* differently. Usually, *C. albicans* are susceptible to amphotericin B.Nonetheless, a number of studies demonstrate that non-*albicans* have a higher resistance to antifungals, particularly fluconazole [127-130]. According to Yang *et al*. [129], the susceptibility of antifungals is linked to their geographic distribution. The treatment of candiduria is still debatable. It has been suggested by clinicians that the *Candida* species found in urine samples indicates a lower UTI or innocuous colonization. Conversely, it is widely recognized that candiduria poses a significant risk for invasive candidiasis, which carries a high morbidity and mortality rate [131]. AmpB and azole are two prominent antifungals that are used clinically to treat candiduria in patients [132,133].A study done by Gayosso*et al.,*they discovered that ampB and ketoconazole have less activity against *C. glabrata* but fluconazole has more [131]. Furthermore, Chen *et al.*and Seifil*et al* stated that entire *Candida* species were fluconazole and amphotericin resistant [134] and all isolates of NAC were resistant to fluconazole while all isolates were sensetive to amphotericin B, clotrimazole, and miconazole [135].Clotrimazole and miconazole sensitivity was found in 67% and 86% of tested isolates, respectively. Toll *et al.* stated that intravascular treatment of clotrimazole to fungal cystitis in a cat. Furthermore, except for fluconazole, *Candida* species were responsive to antifungals [136].In a 2021 study, Pramodhini S *et al* discovered that *Candida* were resistant to 38.6% amphotericin B followed by 22.7% fluconazole, 15.7% caspofungin, and 12.3% of voriconazole. A similar result was reported byMarak*et al.*[137, 138]. Another investigation on the antifungal susceptibility of *Candida albicans* by Yenisehirli*et al* found 34% resistance to fluconazole and 14% resistance to voriconazole [139].

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Despite it is rare, some species of *Candida,* such *C. tropicalis*, have been found to be resistant to caspofungin.The first case of *C. tropicalis* infection with a MIC of 4 g/mL that was clinically resistant to caspofungin was reported by Pasquale *et al.*[143]. Isolates of *C. tropicalis* and *C. parapsilosis* from China and Malaysia have been found to be resistance to caspofungin. [146,147]. Furthermore, during antifungal therapy, Madsen *et al*. detected caspofungin resistance in *C. glabrata*. [144]. Only five isolates (10%), including two strains of *Candida glabrata* and three strains of *Candida albicans*, were found to be resistant to caspofungin (MIC > 2 g/mL), according to various studies. The majority of antifungals usually cause resistant in non-albicans*Candida* species.[140,141,142]. FKS alterations that improved *Candida* species resistance to caspofungin were discovered by Fekkar*et al.*Posaconazole is a triazoles antifungal with activity against several yeasts, numerous saprophytic fungi, and some endemic fungi [145]. Posaconazolewas shown to be effective in a mouse model of hematogenous kidney candidiasis [151]. It has shown efficacy against other NACs, such as *Candida krusei* and *Candida glabrata*, in besides *Candida albicans*[142]. It's in vitro activity against Candida species differs, nonetheless.Accordingly, after incubating for 24 hours, the posaconazole resistance in the isolates of *Candida albicans* and *Candida glabrata* increased from 6% to 12%, although no resistance was found in the strains of *Candida tropicalis* and *Candida krusei*[147]. The majority of the research reveals the relevance of *Candida* species in urine samples from ICU and urology patients. Antifungal drugs also had excellent benefits on diverse forms of *Candida*, although most *candida* species in the patients with candiduria were becoming resistant to various types of antifungal agents.

Conclusion:

In conclusion, there is minimal information available that allows clinicians to categorize predisposing factors for developing "candiduria" in patients. Nonetheless, patients with impaired immune systems are possible risks associated with candiduria, according to the study's findings. Increased incidence and prevalence of candiduria are closely related to both diabetes mellitus and invasive therapy. Candiduria and mortality rates are also largely dependent on the pathogenicity of NAC species and antifungal resistance.Males experienced candiduria more frequently than females, with the mean incidence of the condition among diabetic patients ranging from 15 to 30 percent of the global prevalence rate.Identifying the species of Candida correctly is crucial in these complicated situations to choose the most effective antifungal therapy.Therefore, to aid physicians in providing patients with candiduria with better care, it is important to regularly identify the species of *Candida* and their pattern of susceptibility to antifungals.

AUTHOR'S CONTRIBUTION STATEMENT

Design of the study, manuscript drafting and results evaluation, was done by KHD. In addition to reviewing the manuscript and selections of articles were done by MS & KS. Neha and Rosy drafted the manuscript and reviewed the manuscript.

CONFLICT OF INTEREST

Conflict of interest declared none.

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