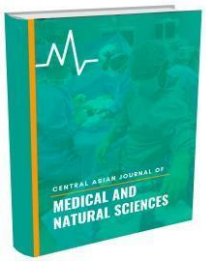

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Article

Identification of *Candida Species* in Patients with Type 2 Diabetes Mellitus in Kirkuk City-Iraq

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Abstract: Patients with type 2 diabetes mellitus (T2DM) are more prone to *Candida* infections due to high blood sugar and weakened immunity. While *Candida albicans* is common, other species are increasingly seen. Identifying these species is important for proper treatment and infection control**.** The present study was conducted at Azadi Teaching Hospital and Kirkuk General Hospital in the city of Kirkuk. A total of 100 oral swabs were collected from patients diagnosed with type 2 diabetes mellitus (T2DM) between November 21, 2021, and March 21, 2022. Samples from individuals who were smokers or suffered from hypertension or other chronic conditions were excluded from the study. The final sample included 50 males and 50 females, with ages ranging between 30 and 60 years. Diabetes was confirmed by hospital physicians prior to sample collection. Direct microscopic examination revealed positive findings in 41 male patients (82%) and 46 female patients (92%). Three Candida species were identified using biochemical tests and culturing on Chrom Agar Candida medium. *Candida albicans* was the most frequently isolated species, accounting for 59 isolates (73.75%), followed by *Candida glabrata* with 13 isolates (16.25%), and *Candida dubliniensis* with 8 isolates (10%).

Keywords: *Candida* spp, Diabetes type 2, CHROM Agar

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1. Introduction

Candida is a genus of unicellular fungi [1], classified under yeast-like organisms [2]. While the genus comprises more than 200 species, only a limited number are considered pathogenic to humans [3]. Among the most clinically relevant species are Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida dubliniensis, with C. albicans being the most prevalent and virulent pathogen [4].

Candida species are part of the normal human microbiota and can be found in various anatomical sites such as the oral cavity, skin, gastrointestinal tract, and vagina [5]. However, under certain conditions, these organisms can shift from commensal to opportunistic pathogens. Predisposing factors include prolonged use of broad-spectrum antibiotics, immunosuppression, disruption of the microbial flora, and local environmental changes such as decreased salivary flow, increased mucosal acidity, or mucosal dryness. Additionally, systemic immunodeficiency states such as HIV/AIDS, diabetes mellitus, and chemotherapy further increase the risk of *Candida* infections [6]. The

clinical manifestations of *Candida* infections vary depending on the site of colonization or invasion, and include:

1. Oral candidiasis (thrush): Characterized by white plaques on the tongue and oral mucosa, sometimes accompanied by erythema and pain. It is frequently observed in infants, immunocompromised patients, and the elderly [7].
2. Vulvovaginal candidiasis: Presents with pruritus, irritation, and abnormal vaginal discharge [8].
3. Cutaneous candidiasis: Typically affects moist intertriginous areas of the skin, especially in individuals with obesity or excessive sweating [9].
4. Systemic candidiasis (candidemia): A severe and potentially life-threatening condition where *Candida* enters the bloodstream and disseminates to internal organs such as the liver, kidneys, heart, or brain. This form is often associated with nosocomial infections in hospitalized patients [10]. Diabetes mellitus is a widely prevalent chronic disease that poses significant health risks to individuals and populations [11]. According to reports published by the World Health Organization in 2000, the global number of individuals affected by diabetes exceeded 171 million, with projections estimating an increase to approximately 366 million by 2030. This rise is largely attributed to changes in lifestyle patterns and factors related to nutrition and obesity [12]. The disease is classified by the World Health Organization into three main types. Type 1 diabetes is characterized by the loss of the body's ability to produce insulin due to the destruction of pancreatic beta cells, and it often manifests at an early age. Type 2 diabetes, which is the most common form, arises from insulin resistance and/or inadequate insulin secretion and is frequently associated with risk factors such as obesity and physical inactivity [13]. Additionally, gestational diabetes is a temporary condition that develops during pregnancy as a result of hormonal changes. Although symptoms typically resolve after childbirth, gestational diabetes is considered a predictor of increased risk for developing type 2 diabetes later in life [14].

Patients with diabetes experience persistently elevated blood glucose levels, which lead to oral complications that increase the susceptibility of the oral cavity to infections [15]. The oral mucosa and saliva contain antimicrobial factors such as lysozyme, which plays a crucial role in protecting the oral cavity from infections, along with the metalloprotein gustin, which contains zinc essential for the continuous maturation of taste buds [16]. However, in diabetic individuals, the oral mucosa undergoes significant alterations and exhibits reduced production of these antimicrobial agents, resulting in decreased tongue hydration and promoting the proliferation of pathogenic microorganisms [17]. Consequently, these patients are at higher risk of opportunistic infections, including oral candidiasis, a superficial fungal infection primarily caused by Candida species and frequently associated with poor glycemic control [18]. This infection predominantly affects the dorsal surface of the tongue, followed by the palate and other areas of the oral mucosa, and is accompanied by symptoms such as taste disturbances, oral numbness, burning sensations, halitosis, and the presence of white patches on the tongue [19,20]

Evidence indicates a correlation between increased Candida albicans colonization and elevated blood glucose levels. Several factors significantly impact the balance between the host and fungal organisms, leading to the transition of Candida from a commensal state to a pathogenic one causing infection. Among these factors, reduced salivary flow, increased glucose concentration in saliva, and impaired neutrophil killing capacity are key contributors to this shift [21]. Additionally, other factors such as tobacco smoking, alcohol consumption, denture use, medication intake, and immunosuppression play a significant role in the development of oral candidiasis [22].

2. Materials and Methods

2.1 Study Samples

The present study was conducted at Azadi Teaching Hospital and Kirkuk General Hospital in the city of Kirkuk. A total of 100 oral swab samples were collected from patients with Type 2 Diabetes between November 21, 2021, and March 21, 2022. Samples from smokers and individuals with hypertension or other chronic diseases were excluded. The sample comprised 50 males and 50 females, with patients' ages ranging from 30 to 60 years. Diabetes diagnosis was confirmed by hospital physicians, while the diagnosis of oral candidiasis was performed at Department of Biology, College of Education for Pure Sciences, University of Kirkuk.

2.2 Oral swabs collection

Oral samples were collected using sterile cotton swabs containing a specialized transport medium. The swabbing was performed gently on the roof of the tongue and the oral mucosal tissues. After sample collection, the swabs were aseptically placed into sterile culture tubes containing the transport medium to preserve sample integrity. The samples were then transported to the laboratory as soon as possible and incubated at 37°C for 24 hours [23].

2.3 Laboratory examinations of samples

Swabs were collected from the oral cavity and analyzed using two different methods:

a. Direct Microscopic Examination

A drop from the swab was collected using the designated stick and placed on a clean glass slide, then covered with a coverslip. The slide was then passed over a flame by moving it back and forth two to three times to fix the specimen. The sample was subsequently examined under a light microscope, initially at 10X magnification and then at 40X, to detect the presence of yeasts and pseudomycelium A second glass slide was also prepared, fixed, and stained using Gram stain, revealing Gram-positive yeast cells The sensitivity of the direct examination was assessed by comparing its results with those of in vitro culture [24]. According to the following equation:

Sensitivity = The number of positive cases x 100

Number of positive cases + number of false negative cases

b. Indirect examination:

The collected swabs were placed in plastic Petri dishes containing solid Sabouraud Dextrose Agar (SDA) supplemented with chloramphenicol, and the inoculated plates were incubated at 37°C for a period ranging from 24 to 48 hours [25].

c. Isolation and Purification:

Individual colonies were obtained from samples previously cultured on solid Sabouraud Dextrose Agar (SDAC) medium and subsequently purified for use in further diagnostic examinations [26].

2.4 Diagnosis

a. Morphological Characteristics:

The external features of the colonies grown on SDAC medium were evaluated, including observation of color, shape, texture, diameter, elevation, and odor of each colony [25].

b. Biochemical Tests

- Growth test on Chrome Agar *Candida* (CAC)

The test was performed by collecting a small portion from a 24-hour-old pure yeast colony that had grown on SDA medium, using a sterile tool. The sample was then inoculated onto Chrome Agar medium. The plates were incubated at 37°C for 24 to 48 hours. Strain identification was carried out according to the manufacturer's instructions, relying on the colony color and morphology to differentiate Candida species as follows:*C. albicans* appears green and *C.tropicalis* appears blue, *C. glabrata* ranges from light pink to creamy, *C. krusei* shows a dark pink color, *C. lusitaniae* ranges from pale pink to purple [27].

- Germ Tube Formation Test (GTT)

In this test, 2 ml of egg white (albumin) is placed into sterile test tubes, followed by the addition of a sample from a pure yeast colony grown on Sabouraud Dextrose Agar (SDA) medium. The tubes are then incubated at 37°C for 2 to 3 hours. After incubation, a drop of the suspension is placed on a sterile glass slide and examined under a light microscope to detect the presence of a germ tube. This test is characteristic of *C. albicans*, where the germ tube appears as a projection growing from one side of the cell, reaching approximately 3 to 4 times the length of the cell itself [28].

- Chlamydospores Forming Test

This test is considered one of the key diagnostic characteristics for identifying Candida species. A single pure colony of yeast, grown on Sabouraud Dextrose Agar (SDA), was collected using a sterile inoculation needle without touching the agar surface. The colony was then streaked onto Corn Meal Agar (CMA) by drawing three parallel lines on the surface of the medium in a Petri dish. Each line was approximately 3.5 cm in length, with a spacing of about 1.2 cm between them. A sterile glass coverslip was carefully placed over the streaked lines on the agar surface. The plates were then incubated at 37°C for 48 hours. After incubation, the coverslip was gently removed using sterile forceps and placed onto a clean glass slide. A drop of Lactophenol Cotton Blue stain was added, and the slide was examined under a light microscope at magnifications of 10x and 40x to detect the presence or absence of chlamydospores, which are indicative of *Candida albicans* [29].

- Testing the ability of *Candida* to grow at a temperature of 45° C

The growth test of yeast at 45°C was conducted according to the method described in reference Samples were inoculated onto Sabouraud Dextrose Agar (SDA) and incubated at 45°C for 48 to 72 hours. This test is intended to differentiate between yeast species that exhibit colony morphology similar to *Candida albicans* on SDA medium [30].

- Test Sugar Fermentation

The sugar fermentation test was conducted by distributing 2 mL of sugar fermentation medium into sterile test tubes, each containing an inverted Durham tube to capture any gas produced. Subsequently, 2 mL of a sugar solution—comprising glucose, sucrose, galactose, lactose, or maltose—was added to each tube. A few drops of phenol red, a pH indicator, were introduced until the medium turned red, indicating a neutral pH. The tubes were then inoculated with a yeast suspension and incubated at 30°C. Observations were made daily over a 10-day period. A positive fermentation result was indicated by a color change from red to yellow, signifying acid production, and the presence of gas bubbles within the Durham tube [31].

- Sugar Assimilation Test

The test was carried out according to the established method. Initially, a medium containing various types of sugars was prepared, poured into Petri dishes, and allowed to solidify completely. Once solidified, 1 mL of a yeast suspension aged between 24 to 48 hours was used to inoculate the surface of the medium using an L-shaped spreader (L-Spreader).Following inoculation, the plates were left for 30 minutes to allow the surface layer to dry. Subsequently, 6 mm diameter wells were made in the inoculated area using a cork borer. Stock sugar solutions—including glucose, sucrose, galactose, lactose, and maltose—were then added into the wells using a micropipette.The plates were incubated at 30°C for a period of 2 to 4 days. During incubation, the wells were monitored to assess the presence or absence of yeast growth [32].

2.5 Ethical statements

The study received approval from the Iraqi Ministry of Health and Environment and was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki.

3. Results and Discussion

Analysis of the isolated samples

Table 1 presents the results of direct microscopic examination and culture on Sabouraud dextrose agar medium for 100 oral samples collected from patients with type 2 diabetes. Direct microscopy revealed that the prevalence of oral candidiasis among males was positive in 41 cases, accounting for 82% of the total 50 samples, while 9 cases (18%) were negative. In females, 46 samples (92%) tested positive out of 50 samples, whereas 4 samples (8%) were negative.

As for the results of the laboratory culture, the prevalence of oral candidiasis among males was positive in 37 cases, representing 74% of the total 50 samples, while 13 cases (26%) were negative. In females, the study showed that 43 samples (86%) tested positive for oral candidiasis out of 50 samples, whereas 7 samples (14%) were negative.

Table 1. Culture Results Among Males and Females.

Type of Test \ Test Result	Gender	Positive samples	Percentage	Negative samples	Percentage
Direct microscopy	**Male (50)**	41	% 82	9	% 18
	Female (50)	46	% 92	4	% 8
In vitro culture	**Male (50)**	37	% 74	13	% 26
	Female(50)	43	% 86	7	% 14

The results presented in Table 1 indicate that women are more susceptible to oral candidiasis [33]. due to several factors. These include: 1- hormonal influences, particularly the elevated levels of estrogen and progesterone, which tend to rise significantly during menstruation; 2- the use of cosmetic products and topical medications; and 3- the use of oral contraceptives [34]. Additionally, in postmenopausal women, salivary flow tends to decrease, leading to xerostomia (dry mouth), a condition that favors the overgrowth of *Candida*, as saliva functions as a natural antifungal agent [35].

Identification of Isolated Yeasts

The genus *Candida spp.* was identified based on cultural characteristics, microscopic morphology, and the results of biochemical tests. To enhance diagnostic accuracy, Chrom Agar Candida (CAC) was employed as a preliminary medium for the presumptive identification of *Candida* species [25].

Culture-based diagnosis

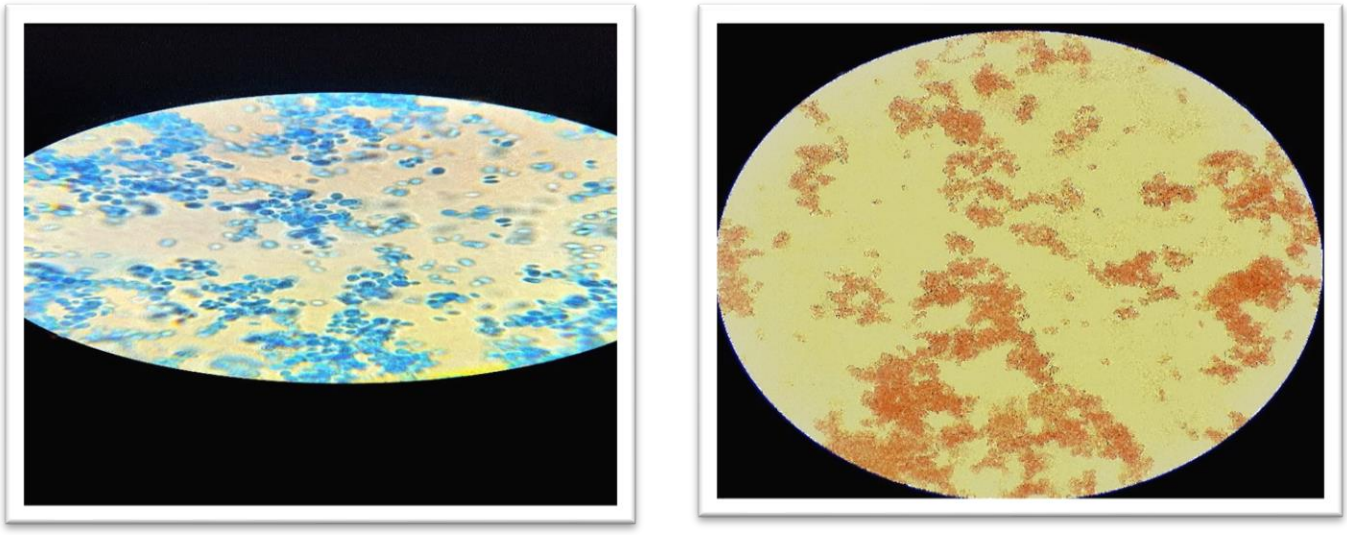
Candida spp. isolates exhibited a characteristic growth pattern when cultured on the commonly used medium, Sabouraud Dextrose Agar. The colonies appeared white to milky in color, with a smooth surface, convex shape, and noticeable glossiness, accompanied by a distinctive odor. Incubation was carried out at 37°C for a period ranging from 24 to 48 hours, as illustrated in Figure 1.

Figure 1. Growth of *Candida albicans* isolate on SDA medium at 37°C for 24–48 hours.

This finding is consistent with the results of several researchers, as fungal colonies appeared white when cultured on Sabouraud Dextrose Agar [36]. The increased fungal growth observed in diabetic patients can be attributed to several factors, including: 1- Decreased salivary secretion, which may result from frequent urination, leads to a reduction in the immune function of saliva 2 - Replacement of normal glandular tissue with adipose tissue in the major salivary glands 3- Accumulation of glucose in tissues creates a favorable environment for fungal growth and proliferation 4- Elevated glucose levels may enhance *Candida* adhesion to oral epithelial cells through the formation of glycosylated bonds with tissue proteins; the accumulation of these glycosylation products increases the availability of *Candida* binding receptors [37].

Microscopic Diagnosis

The results presented in Figure 2 demonstrated that the cells exhibited various morphologies, including single elongated and branched forms, as well as spherical to oval shapes. Lactophenol cotton blue and Gram stains were used to stain the cells prior to microscopic examination.



A **B**

Figure 2. Illustrates *C. albicans* yeast colonies stained with two different dyes: (A) lactophenol cotton blue and (B) Gram stain, examined under 40X magnification.

The results showed that yeast cells were more distinctly visualized when stained with Gram stain compared to lactophenol cotton blue stain [38]. This is attributed to the cell wall's ability to retain the Gram stain due to the presence of a peptidoglycan layer, which fixes the blue color. The outer cell wall is composed of various components,

including polysaccharide chains such as glucans, chitin, and glycoproteins known as mannoproteins [39].

Biochemical Tests To Diagnose *Candida* spp.

Diagnosis using Chromagar Medium

This medium is considered one of the modern and efficient techniques for the rapid identification of different *Candida* species, based on the variation in colony color. A total of 80 fungal isolates obtained from the oral cavities of patients with type 2 diabetes mellitus were inoculated onto the medium and incubated at 37°C for 24–48 hours. As shown in Figure (3), the results demonstrated clear color differentiation among the species: *C. albicans* exhibited a light green coloration, *C. glabrata* appeared purple, and *C. dubliniensis* developed dark green colonies. These observations are consistent with the findings of [40], and also align with the color specifications provided by the manufacturer of the chromogenic medium. Additionally, Table 2 illustrates the frequency distribution of the isolates. *C. albicans* was the most prevalent species, with 59 isolates (73.75%), followed by *C. glabrata* with 13 isolates (16.25%), and *C. dubliniensis* with 8 isolates (10%). This high prevalence may be attributed to inadequate oral rinsing practices, particularly the lack of water use during mouth cleaning, which contributes to the retention and dissemination of pathogenic oral microorganisms [41].

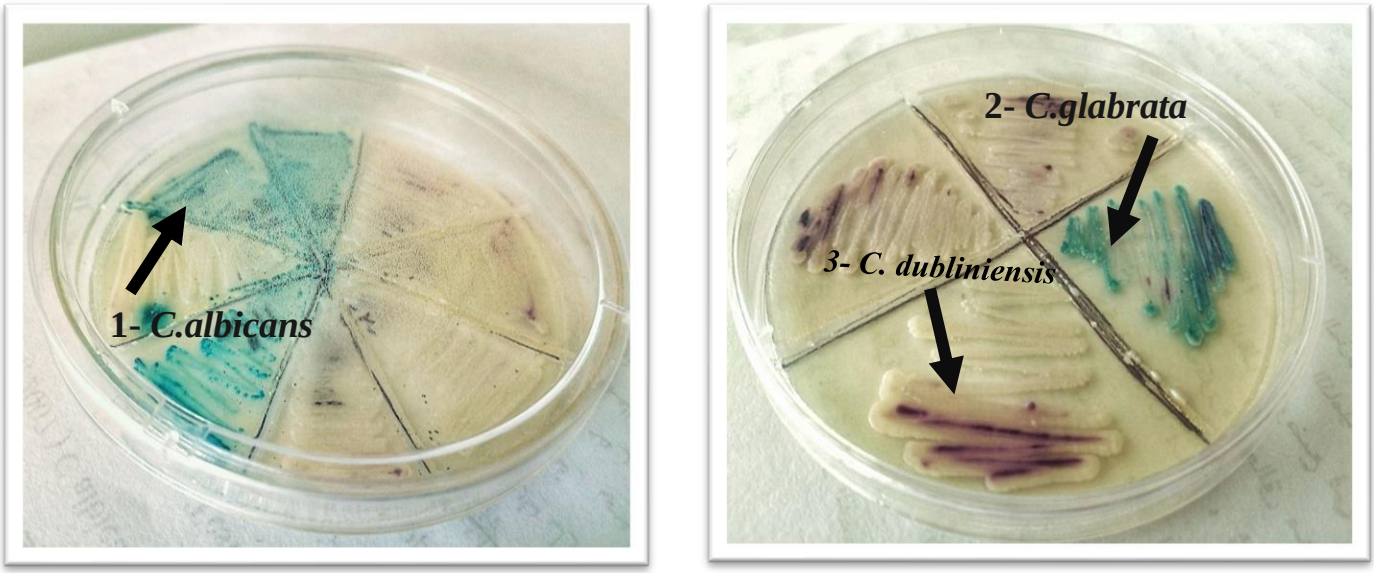


Figure 3. Identification of *Candida* spp. on Chrom Agar medium incubated at 37°C for 24–48 hours.

Table 2. Number and Percentage of *Candida* Species Isolated During the Study.

Species of *Candida*	Number of species	Prevalence rate
Candida albicans	59	73.75%
Candida glabrata	13	16.25%
Candida dubliniensis	8	10%
Total	80	100%

Germ Tube Formation Ability of *Candida* Species

The data presented in Figure 4 and Table 3 indicate that *Candida albicans* was the only species among those studied that exhibited the ability to form germ tubes under the same experimental conditions, whereas the other species did not show this capability

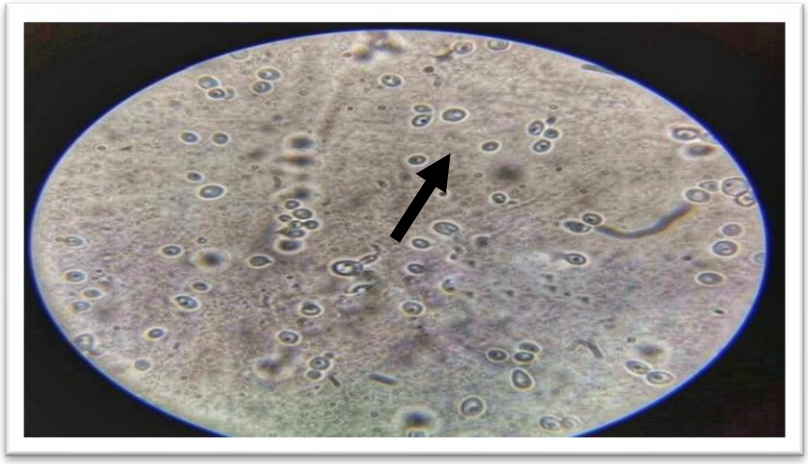


Figure 4. Germ Tube Formation in *Candida albicans* (Magnification 40X).

These findings are consistent with those reported by [42], who demonstrated that *Candida albicans* is the only species capable of forming germ tubes— a characteristic considered diagnostic for this species. In contrast, the other *Candida* species did not exhibit this trait. It is estimated that approximately 95% of *C. albicans* isolates produce germ tubes when stimulated with serum, which acts as an inducer for their formation. The germ tube appears as a long extension emerging from the surface of the yeast cell and plays a critical role in penetrating the epithelial tissues of the host. Within these tissues, the organism grows in the form of pseudohyphae, facilitating invasion and eventual entry into the bloodstream. Furthermore, some studies suggest that germ tube formation is essential for the nutritional acquisition of the yeast cell [43].

Chlamydospore Formation Capability in *Candida* Species

As illustrated in Figure 5 and Table 3, all *Candida albicans* isolates demonstrated the ability to produce chlamydospores when cultured on Corn Meal Agar (CAM) medium.

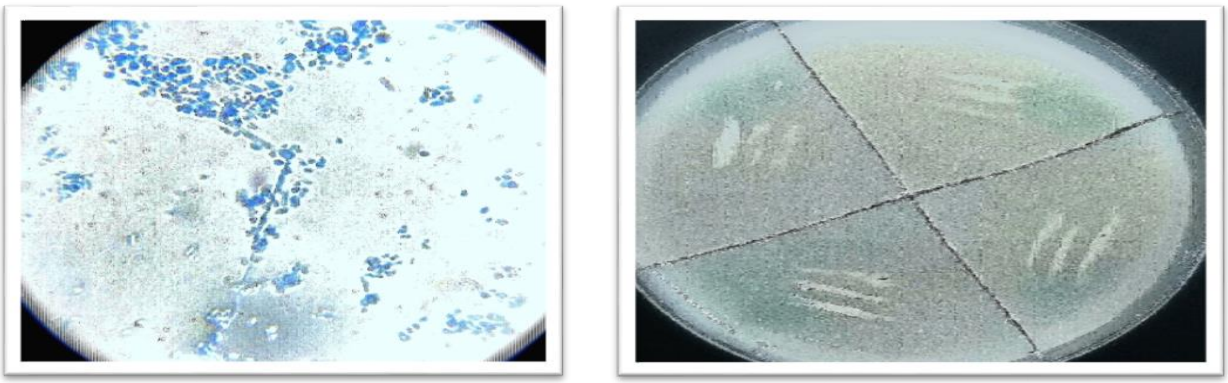


Figure 5. Formation of Chlamydospores by *C. albicans* on Cornmeal Agar at 40X Magnification.

These findings are consistent with those reported by [38], who demonstrated that *Candida albicans* is capable of forming chlamydospores when cultured on Corn Meal Agar, a characteristic feature used for the identification of this species. Chlamydospores are characterized by their large size, thick walls, and round shape, typically found at the tips of fungal hyphae. They may occur singly or clustered. The formation of these spores is attributed to nutrient-limited growth conditions, leading to yeast starvation, as well as the unfavorable environment provided by this medium, which is described as a yeast starvation medium [26].

Growth Test at 45°C

As shown in Figure 6 and Table 3, the results of the growth test at 45°C indicated that *Candida albicans* was the only species capable of growing under these conditions, whereas the other species were unable to tolerate this temperature.

Figure 6. Growth of *C. albicans* Isolate at 45°C.

This result is consistent with the findings of [42], who reported that the ability to grow at elevated temperatures is a distinguishing characteristic between *Candida albicans* and *Candida dubliniensis*, with the latter lacking this trait. The thermotolerance observed in *C. albicans* is attributed to its classification as a thermophilic fungus [44].

Table 3. Selected Biochemical Tests of the Studied Isolates.

Types of candida	germ tube formation	Chlamydia spore formation	Growth at temperature	
			37°C	45°C
C.albicans	+	+	+	+
C.dubliniensis	–	–	+	–
C.glabrata	–	–	+	–

Carbohydrate Fermentation and Assimilation by *Candida* Species

The results of the carbohydrate fermentation test, as presented in Table (4) and Figure (7), showed that a color change of the medium from red to yellow, along with the production of gas bubbles in the Durham tubes, indicates a positive reaction. In contrast, no color change signifies a negative result. The findings revealed that *Candida albicans* isolates were capable of fermenting glucose, maltose, and galactose, but were unable to ferment sucrose and lactose. Additionally, they demonstrated the ability to assimilate most sugars except galactose and lactose. These observations are consistent with the findings of [45] , who reported that all *C. albicans* isolates could ferment glucose, galactose, and maltose, but not sucrose or lactose.Isolates of *Candida dubliniensis* were found to ferment and assimilate most tested carbohydrates, including glucose, galactose, sucrose, and maltose, but failed to utilize lactose. On the other hand, *Candida glabrata* isolates exhibited limited capability, being able to ferment and assimilate only glucose, with no activity toward galactose, lactose, sucrose, or maltose. These results are in agreement with the findings of [42], who noted that *C. glabrata* was able to ferment glucose exclusively and could not metabolize the other tested sugars.Overall, the data suggest that most isolates preferentially utilize glucose due to its simple structure and high energy yield. *C. albicans*, in particular, demonstrated a broad capacity to metabolize various carbohydrates, which may explain its high prevalence among the identified isolates [46]. The inability of all isolates to ferment lactose is likely due to the absence of βgalactosidase enzyme, which is required to hydrolyze lactose into glucose and galactose for assimilation [47].

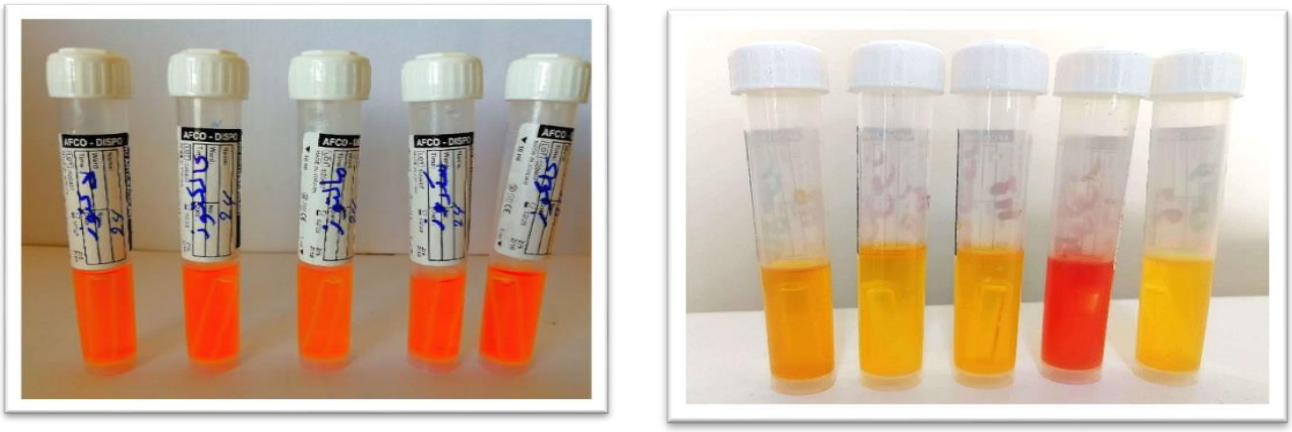


Figure 7. Sugar Fermentation Test.

Surface Growth Ability of Candida Species

As illustrated in Figure 8 and Table 4, the results of the surface growth test demonstrated that *Candida albicans* and *Candida dubliniensis* possess the ability to produce creeping surface growth that extends along the medium and up the inner walls of the test tube containing liquid Sabouraud Dextrose Broth. In contrast, *Candida glabrata* isolates did not exhibit similar surface growth under the same experimental conditions.

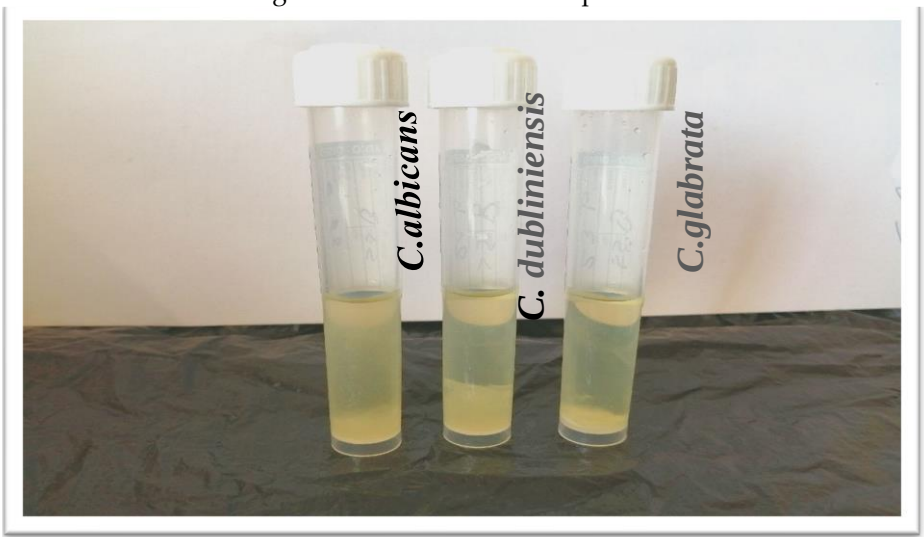


Figure 8. Surface Growth of *C. albicans* and *C. dubliniensis* on SSB Medium.

Table 4. Biochemical Tests for the Identification of *Candida albicans*.

Types of candida	Sugar Fermentation					Sugar Assimilation					Surface growth
	Glu	Gal	Suc	Lac	Mal	Glu	Gal	Suc	Mal	Lac	
C.albicans	+	+	-	-	+	+	-	+	+	-	+
C.dubliniensis	+	+	v	-	+	+	+	v	+	-	+
C.glabrata	+	-	-	-	-	+	-	-	-	-	-

4. Conclusion

The rise in type 2 diabetes in the blood leads to the growth of many microorganisms, including the oral candida fungus, which grows due to the high glucose of saliva because the fungal biofilm when it comes into contact with the sugar-rich mucous membrane leads to an overgrowth of fungi in the mouth, The rise in type 2 diabetes in the blood and the growth of fungi cause a decrease in the body's immunity.

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