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ORIGINAL RESEARCH

The Effect of *Quercus robur* Bark on Oral Candidiasis Caused by *Candida albicans* and *Candida glabrata* Isolated from a Pediatric Oral Infection as Comparison to Azole Antifungal

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Background: The original diversity of *Quercus rubra* L. (oak) is in eastern America and then distributed to European districts. Oral candidiasis is the most common fungal infection among humans. Azole antifungal drugs can be used to treat Candida infection. *Candida albicans* and *Candida glabrata* have emerged as the most common pathogenic yeasts in cases of oral candidiasis.

Aim of the Study: This study aimed to explore the genotype *Candida* spp. and evaluate the antifungal activity of hot water extract of oak bark against *C. albicans* and *C. glabrata* as an alternative pharmacotherapy compared to azole antifungal agents.

Materials and Methods: The sample was isolated from an 8-year-old child with aggressive oral candidiasis and identified by culturing on sabouraud dextrose agar (SDA) CHROMagar. Genotyping of *Candida* spp. was performed using the internal transcribed spacer (ITS) region. Standard discs of the antifungal's fluconazole, itraconazole, ketoconazole 10 mg/L for each, amphotericin 100, nystatin 50 mg/L, and hot water oak bark extract were administered to *C. albicans* and *C. glabrata* in vitro.

Results: Genotyping of *Candida* spp. showed that 98% of oral candidiasis cases were *C. glabrata* which had an 870 bp genotype, while 2% were *C. albicans* which had a 550 bp genotype based on ITS barcoding region size. The findings that the oak bark extract had high antifungal activity against *C. glabrata* showed an inhibition zone diameter of 3.067 mm compared to high resistance to antifungals.

Conclusion: Oak extract is considered a successful alternative for the treatment of oral candidiasis infections by antifungals such as azole and nystatin in children.

Keywords: azole antifungal, *C. albicans*, *C. glabrata*, *Candida* genotyping, oak bark activity

Introduction

Quercus rubra L. (oak) is a member of the Fagaceae family and is widely distributed in Eastern America, and European districts.[1–3] Most studies have indicated that numerous plant species produce extracts with highly active bioactive compounds, such as tannins, saponins, and alkaloids.[4] Oak trees are a significant source of antifungal compounds that have been evaluated for their biological properties.[5,6]

Oral Candidiasis poses a significant clinical health challenge, affecting more than 300 million individuals annually.[7–11] It is one of the most expedient fungal infections that can affect the oral cavity of patients. *Candida* can aggregate on the normal oral biota of healthy persons in the area of the oral cavity, as reported in previous studies in 45–65% of healthy infants, while in healthy adults was 30–55%.[12] In addition, candidiasis, which results from systemic and local factors, can

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develop and lead to symptoms inside the mouth.[13] More than 150 species of *Candida* have been found and explained previously, but oral candidiasis is caused by the overgrowth of *Candida albicans* in the mouth. Other species such as *Candida glabrata* "currently reclassified as Nakaseomyces glabratus", *Candida tropicalis, Candida parapsilosis, Pichia kudriavzevii*, and *Candida dubliniensis* can cause infections inside the mouth.[14]

The reason for including the genotype of candida was to determine precisely the type of candida species that can be given the enhancement in the recognition of the variations at the level of species of candida in the antifungal resistance and pathogenicity of candida.[15]

Antifungal resistance presents a challenge for healthcare providers managing invasive fungal infections owing to the limited available options for antifungal medications. Moreover, existing drugs may be hindered by drug interactions and severe side effects, which restrict their long-term use or dosage increase. Several studies have reported a low susceptibility of *Candida* species to azole antifungals "which are commonly used in clinical practice". This is especially concerning in pediatric patients, due to their developing immune systems and the limited number of antifungal agents approved for use in children.[16,17]

Recent assays for the identification of *Candida* spp by molecular methods and antifungal resistance have provided accurate results.[18] Thus, the purpose of this study was to evaluate the activity of the hot water extract of oak bark as an alternative antifungal therapy against *C. albicans* and *C. glabrata* compared with azole.

Materials and Methods

One case of aggressive oral candidiasis was collected from an 8-year-old patient attending a private outpatient clinic in B. Province on 11 March 2024. The author hereby declares that every action has been assessed and given approval by the ethical principles that were performed in accordance with the ethical standards laid down by the Declaration of Helsinki, 1964. Ethical approval was granted by the Scientific Committee of the College of Dentistry at Mustansiriyah University (no. 777) on March 5, 2024. The patient and his parents were informed of the details of the study and its purpose, and their agreement was obtained for the publication of the data related to the results of the sample taken. The study was conducted between [March, 2024] and [June, 2024].

The bark of *Quercus robus* L. was collected from the herbal medicine market. Originally, the plant barks were collected from the stem of Q. robus trees which were cultivated in Amedi of Kurdistan, Iraq. 36° 55′ 0″ N, 44° 2′ 0″ E. The trees are 35 years old. The identity of oak bark (*Q. robus*) was confirmed by Prof. Dr. Huda Jasim M. Altameme senior of plant taxonomy at, the biology department, University of Babylon. A voucher specimen has been deposited at the national herbarium with reference number 9836, Babylon, Iraq.

This sample was collected using a sterile toothbrush, immersed in sabouraud dextrose medium (SDA) (Himedia, India), and then incubated at 30°C for 24/48 h.

Purified individual colonies on SDA were streaked on CHROMagr (Himedia, India) and incubated for 24–48 h.[19] Pre-identification was conducted based on the CHROMagar colored key designed by Nadeem et al in 2010.[20]

Fifteen *Candida* spp. isolates were genotyped using the internal transcribed spacer (ITS) barcoding region. Direct culture of polymerase chain reaction (PCR) of 15 pure colonies from colony profiles grown on SDA, which were selected randomly, and a tiny portion of each colony was taken by tip 0.2 mL and picked up directly in a cocktail of PCR. The universal primer pair was designed to target specific sequences of the ITS rRNA region of *Candida* spp., according to Imran and Hadeel in 2014.[19]

The primer pairs used were ITS5-ITS4 (5′-GGAAGTAAAAGTCGTAACAAGG-3′) and reverse (5′-TCCTCCGCTTATTGATATGC-3). The PCR reaction (25 µL) contained 5 µL of 20× Master Mix (Promega), 2 µL (10 pemole) of each primer, and 1 µL template DNA, with molecular-grade water added to bring the total volume to 25 µL.

The PCR mixture was subjected to amplification with a thermal cycler PCR System (Labnet, USA) under the following conditions: first denaturized at 95°C for 5 min then 30 cycles of initial denaturation at 95°C for 30s, annealing at 56°C for 90s, extension at 72°C for 60s, and extension at 72°C for 10 min.

The PCR products were separated on an agarose gel (1.2%) (Bio Basic Canada Inc.). In addition, electrophoresis was conducted at (100 V) using Tris Borate EDTA Ethylenediamine tetra acetsacide, and the agarose gel was pre-stained with

ethidium bromide (EB) (0.05%). All DNA bands were detected using a desktop gel imager (Ultraviolet UV) Transilluminator (USA).

A disk diffusion (DD) assay following the manufacturer's instructions was conducted using discs with a diameter of 0.4 mm of fluconazole (FLU), itraconazole (ITR), and ketoconazole (KET) (10 mg/L for each). Amphotericin (AMP) 100 and 150 µL of hot water of oak extract were placed into a well (0.5 mm). The oak barks were collected from the herbal medicine market in Babylon City. The collected oak bark samples underwent morphological identification and authorization at the herbarium of the biology department, University of Babylon, Iraq.

Based on standard culturing methods, three CHROMagar Candida plates were used per treatment as replicates. The SDA plates were inoculated with cell suspension (1×10^6) of *C. glabrata* and *C. albicans* for each. The plates were left for 30 min to absorb the liquid and were incubated for 24 h at 30 °C. After 24 h of cultivation, the diameter of the inhibitory zone (dz) was calculated based on the method described by Barry et al in 1979.[21] The diameters of the zones were orthogonally measured using a rural metric. The arithmetic mean of the diameters of the inhibition zones was calculated using a simple statistical method. The data from the study were analyzed using SPSS version 29 (IBM, USA). Mean values and *t*-tests were employed to evaluate the inhibition zones of *C. glabrata* and *C. albicans* in response to activated oak and other antifungal agents.

Results

Cultural Identification

All colonies grown on SDA showed a creamy color, and some showed internal sector growth. Figure 1A, shows the detailed colony texture of SDA. CHROMagar test results: 98% of *Candida* isolates streaked on CHROMagar medium showed a pale reddish color which was pre-identified as *C. glabrata*, whereas only 20% of isolates showed an apple green color which identified *C. albicans* (Figure 1B).

Molecular Genotyping

The results of amplification of ITS1-5.8S-ITS2 with flanking primer sequence by ITS5/ITS primer pair showed that 12 isolates given pale reddish color gave 870 bp bands, indicating that these isolates were *C. glabrata*, while two isolates which gave apple green color shown 550 bp (Figure 2).

The biological activity of antifungal drugs— FLU, ITR, nystatin (NYS), KET, and AMP—generally demonstrated lower inhibitory effects against *C. glabrata* with inhibition values of 0.403 mm, 0.9 mm, 0.733 mm, 1.127 mm, 0.72 mm, respectively, and *C. albicans* (2.1 mm 0.403 mm, 0.4 mm, 2.633 mm, 0.4 mm), respectively, compared to the oak bark

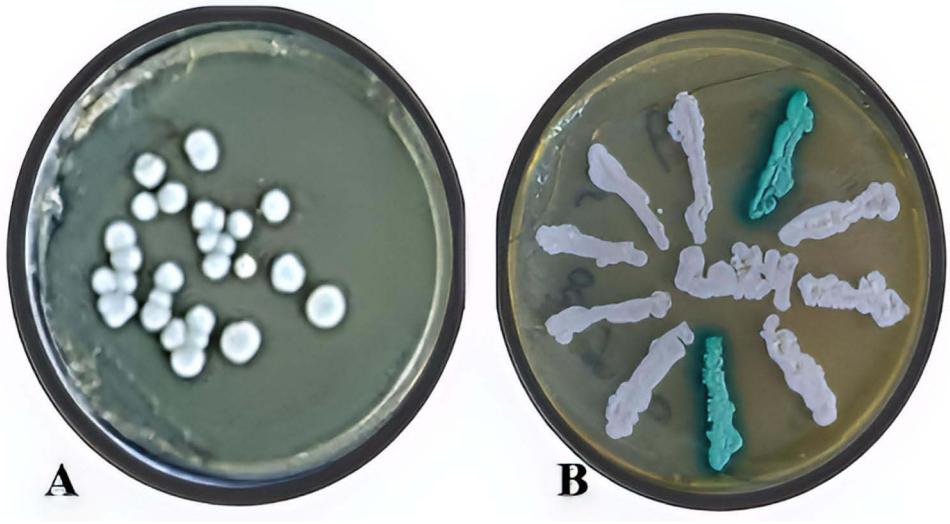

Figure 1 (**A**) Oral *Candida* spp. grown on SDA, (**B**) CHROMagar assay, eight isolates showed a pale reddish color as *C. glabrata* and two isolates showed apple green color as *C. albicans*.

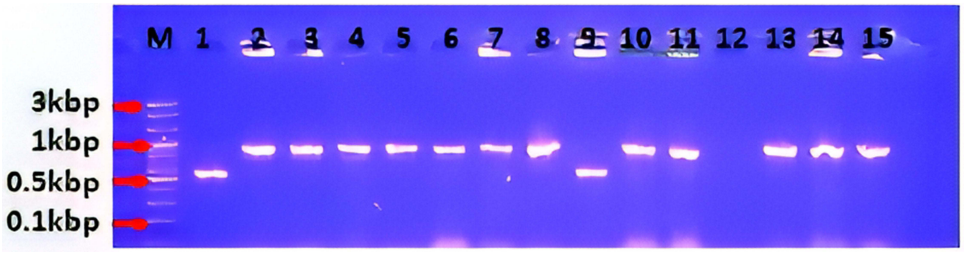

Figure 2 Gel electrophoresis of PCR of ITS1-5.8S-ITS2 profile. 1,9=*C. albicans* (550 bp),2–8,10-1,13–15 *C. glabrata* (870 bp). 1% agarose TBE buffer, 100 volts, 45 min. M, molecular marker 100–30000 bp).

extract. In contrast, the oak bark extract exhibited a high inhibitory action against both *C. glabrata* and *C. albicans*, and the average zone of inhibition was 3.067 mm and 2.290 mm, respectively, higher than the biological activity of standard antifungal discs. *C. glabrata* showed high resistance to antifungal agents, whereas *C. albicans* showed sensitivity to fluconazole and ketoconazole but resistance to other antifungal agents (Table 1 and Figure 3). The DD extract showed low inhibitory activity against both *C. glabrata* and *C. albicans*, while the hot water extract of oak bark showed high antifungal activity against both yeasts under interest (Figure 4A and B).

The findings of this study suggested that extracts from natural ingredients, such as *Quercus robur* bark, can be more effective than traditional antifungal medications against *Candida* species (the novelty). This is particularly beneficial and promising for developing plant-based alternatives for treating oral candidiasis, especially in patients resistant to current antifungal therapies.

Table 1 Statistical Analysis of Inhibition Zones Profile Growth of *C. Glabrata* and *C. Albicans* in vitro Under Activities of Oak and Antifungals

	Fungi	Mean	SD	t-test	p-value
FLU	*C. glabatra*	0.403	0.006	29.338	0.0001**
	C. albican	2.100	0.100		
Oak	*C. glabatra*	3.067	0.058	3.739	0.020*
	C. albican	2.290	0.355		
ITR	*C. glabatra*	0.900	0.100	8.588	0.001**
	C. albican	0.403	0.006		
NYS	*C. glabatra*	0.733	0.058	10.000	0.001**
	C. albican	0.400	0.000		
KET	*C. glabatra*	1.127	0.021	16.928	0.0001**
	C. albican	2.633	0.153		
AMP	*C. glabatra*	0.720	0.010	55.426	0.0001**
	C. albican	0.400	0.000		

Note: significant = *≤0.05, **≤0.01.
Abbreviations: Flu, fluconazole; OAK, *Quercus robur* bark extract; ITR, itraconazole; NYS, nystatin; KET, ketoconazole; AMP, amphotericin; SD, standard deviation.

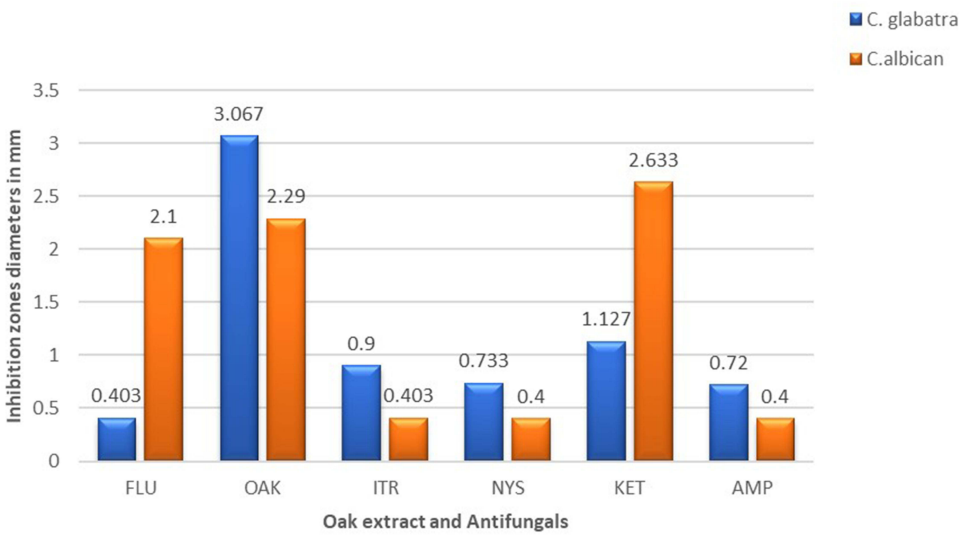

Figure 3 Histograms of inhibition zones profile growth of *C. glabrata* and *C. albicans* in vitro under activities of Quercus robur bark extract (Oak) and antifungals: Fluconazole (Flu.), Itraconazole (Itr.), (Ket) (10 mg/l for each), Amphotericin (Amp.) 100, Nystatin (Nys.).

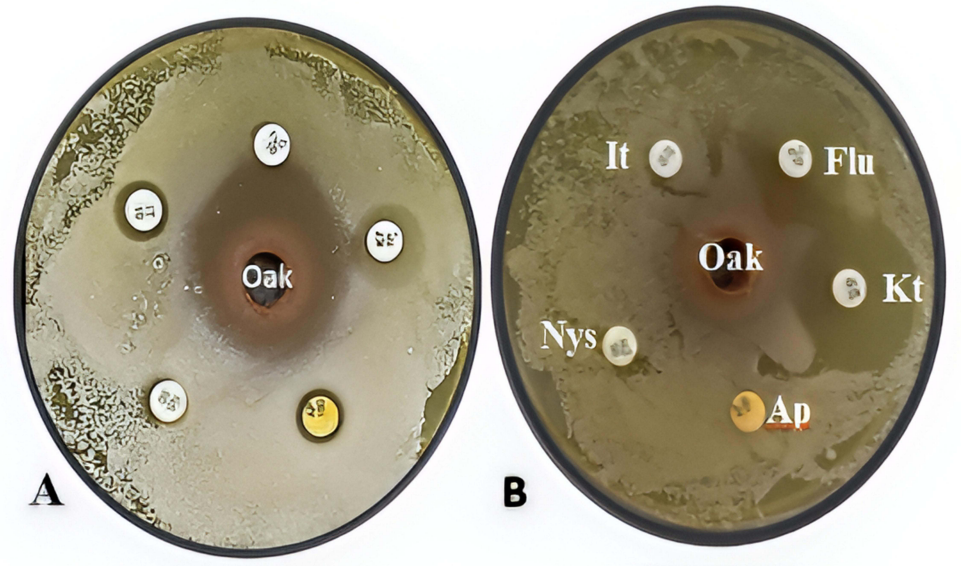

Figure 4 (**A**) Biofilm of *C. glabrata* grown on Sabouraud Dextrose Agar., illustration of the Diameter of inhibitor activity of Oak bark extract (Oak) compared with many antifungals, (**B**) Biofilm of *C. albicans* grown on Sabouraud Dextrose Agar., illustration the Diameter of inhibitor activity of Oak bark extract (Oak) compared with many antifungals. Fluconazole (Flu.), Itraconazole (Itr.), Ketoconazole (Ket) (10 mg/l for each). Amphotericin (Amp.) 100, Nystatin (Nys.), and 150µL of hot water of Oak extract were picked up into a well 0.5 mm, after duration growth of 24h at 30°C.

Discussion

One way to identify the mechanisms of antifungal drug resistance is to compare resistant clinical isolates with their susceptible counterparts.[22] Several studies have reported the resistance of *Candida* spp. to azole drug.[23–25] This study proved that alternative natural plant extract products still possess antifungal activity that confers azole resistance. The results of this study focused on the role of the crude *Quercus robur* bark extract had antifungal activity against *C. glabrata* and *C. albicans* isolates in vitro.

One of the mechanisms of action of *Quercus robur* bark extracts is that these extracts may contain bioactive compounds like phenolic acids, tannins, and flavonoids that can disrupt the walls of the cells of the candida and alter the permeability of the wall.[26] The other mechanism may be the interference with the enzymatic activity of the candida.

Both mechanisms can be discussed in the effectiveness of the extract against the *Candida* species that have resistance to azole or nystatin.[27]

These results are consistent with those reported by Morales in 2021.[6] They reported that oak has antimicrobial, antiproliferative, and immunomodulatory activities. In 2022, Tanase et al[28] referred to the importance of active compounds in an oak extract that had high antibacterial and antifungal activities against bacteria and *Candidia* spp. *C. albicans*, which led to the failure of management of candidiasis with antifungal agents, our interpretation aligns with that of Zarrinfar et al,[29] showed some resistance to azole as an antifungal agent in *C. glabrata* and *C. krusei* following extended exposure to these antifungal agents.

Previous studies have shown that tannins in *Quercus* bark extracts contain significant antibacterial compounds such as vescalagin, ellagic acid, gallic acid, and castalagin.[30,31] This supported our results that showed a potential antifungal effect on crude material metabolites present in *Q. rubra* bark extracts. This is supported by the smaller inhibition diameter zone observed in vitro compared with standard antifungal discs. Similar to findings from another study on *Q. robur* bark extract against *C. albicans* using agar diffusion.[32] Elansary et al[33] also confirmed the antifungal properties of bark extracts of *Q. robur* against *Penicillium funiculosum, Aspergillus flavus, P. ochrochloron*, and *C. albicans*, which correlated with the presence of flavan-3-ols, ellagic acid, and derivatives of caffeic acid in oak bark.[33]

Many clinicians complain of the nothingness of antifungal drugs against human fungal infections, the key priorities of which are antifungal resistance reduction and the quest for innovative antibacterial and antifungal agents able to modulate the virulence *of Candida* spp., such as adhesiveness and biofilm formation. Many studies have reported that secondary metabolites of plants, particularly polyphenols, exhibit antibacterial and antibiofilm properties.[34]

The rise in flu resistance among non-*C. albicans* species is particularly alarming because of the growing number of infections caused by these species globally and the increasing prevalence of resistance to this commonly used azole in many medical facilities. Furthermore, there has been a documented increase in *C. glabrata* resistance to echinocandins in various US institutions, with a higher proportion of these isolates showing resistance to azole.[16]

The final findings and conclusions of this study are a comprehensive note of the biological activities exhibited by *Quercus* extract compounds. Therefore, *Quercus* extracts are considered valuable sources of antifungal activity. The antifungal effects of *Quercus* bark can be largely attributed to new synthetic antifungals or a new combination of oak bark extract and azole drugs. These studies should also focus on developing innovative techniques to combat multidrug resistance and activity of the "quorum sensing", particularly in the formation of *Candida* spp. biofilm. Consequently, in future studies, greater emphasis should be placed on in vivo experiments. Further research is required to establish the relationship between chemical compounds and bioactivity as well as to elucidate their mechanisms of action. Although *Quercus* products are generally considered safe, additional toxicological data are required to ensure their safety profile.[35]

The results of this study indicate that *C. glabrata* and *C. albicans* showed the highest rates of resistance to antifungal medications. Furthermore, *C. glabrata* showed a lower rate of sensitivity to ketoconazole, whereas *C. albicans* exhibited the highest level of sensitivity to ketoconazole and fluconazole. Future studies with larger sample sizes and more isolated colonies and *Candida* spp. are recommended.

Generally, this study was limited to an isolated sample and suggested more investigation to identify the Minimum Inhibitory Concentration (MIC) value.

Conclusion

The oak extract may be considered an alternative treatment for oral candidiasis that is infected by different types of Candida, such as *C. glabrata* and *C. albicans* which can compare positively more than other antifungals (eg azole or nystatin), these findings are preliminary and based on a limited number of isolates. This can open the door for further exploration to develop other antifungal treatments that can be used in patients resistant to oral candidiasis.

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Disclosure

The authors declare no conflict of interest.

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