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Research Article

Identification and Antifungal Susceptibility of Candida Species in Canine Oral Flora

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ABSTRACT

In this study, the presence of *Candida* species was investigated in 60 oral swab samples collected from dogs. The samples were cultured on *Candida* chromogenic agar and incubated at 30°C for 48 hours. At the end of the incubation period, growth was observed on 30 (50%) of the plates and 57 *Candida* colonies were isolated. These colonies exhibited growth as single or multiple agents on the chromogenic agar. Species identification was performed based on the colour patterns displayed on the chromogenic agar, leading to detected of six distinct *Candida* species. Among the isolates, 16 (28.1%) were identified as *Candida krusei*, 10 (17.5%) as *Candida glabrata*, 10 (17.5%) as *Candida parapsilosis*, 9 (15.8%) as *Candida utilis*, 7 (12.3%) as *Candida tropicalis*, and 5 (8.8%) as *Candida albicans*. To confirm their identification at the molecular level, all isolates were verified as belonging to the *Candida* genus using PCR with ITS3-ITS4 primers. The antifungal susceptibility of the isolates (n=57) was assessed using the disk diffusion method. The results revealed that the isolates exhibited resistance to miconazole (43.8%), ketoconazole (26.3%), flucytosine (100%), and fluconazole (93.1%), while showing high sensitivity to nystatin (93.1%). This study highlights the presence of *Candida* species in the oral flora of dogs and underscores the emergence of antifungal resistance among these isolates. The findings suggest that the presence of *Candida* species in the oral microbiota of dogs could pose a potential health risk to both animals and humans, particularly in immunocompromised individuals.

Keywords*: Antifungal, Candida, chromogenic agar, dog, identification.*

Köpek Oral Florasındaki Candida Türlerinin İdentifikasyonu ve Antifungal Duyarlılıkları

ÖZET

Bu çalışmada, köpeklerden toplanan 60 oral sürüntü örneğinde *Candida* türlerinin varlığı araştırıldı. Örnekler *Candida* kromojenik agarına ekildi ve 30°C'de 48 saat inkübe edildi. İnkübasyon süresinin ardından, petrilerin 30'unda (%50) üreme gözlendi ve 57 *Candida* kolonisi izole edildi. Bu koloniler kromojenik agarda tekli veya çoklu etken olarak üreme gösterdi. Tür tanımlaması, kromojenik agarda görüntülenen renk farklılıklarına göre yapıldı ve altı farklı *Candida* türü tespit edildi. İzolatlar arasında 16 (%28,1) *Candida krusei*, 10 (%17,5) *Candida glabrata*, 10 (%17,5) *Candida parapsilosis*, 9 (%15,8) *Candida utilis*, 7 (%12,3) *Candida tropicalis* ve 5 (%8,8) *Candida albicans* olarak tanımlandı. Moleküler düzeyde tanımlanmalarını doğrulamak için tüm izolatların ITS3-ITS4 primerleri ile PCR kullanılarak *Candida* cinsine ait olduğu doğrulandı. İzolatların (n=57) antifungal duyarlılığı disk difüzyon yöntemi kullanılarak değerlendirildi. Sonuçlar izolatların mikonazole (%43,8), ketokonazole (%26,3), flusitozine (%100) ve flukonazole (%93,1) direnç gösterirken, nistatine (%93,1) yüksek duyarlılık gösterdiğini ortaya koydu. Bu çalışma, köpeklerin ağız florasında *Candida* türlerinin varlığını vurgulamakta ve bu izolatlar arasında antifungal direncin ortaya çıktığını vurgulamaktadır. Bulgular, köpeklerin ağız mikrobiyotasında *Candida* türlerinin varlığının, özellikle bağışıklık sistemi baskılanmış bireylerde hem hayvanlar hem de insanlar için potansiyel bir sağlık riski oluşturabileceğini düşündürmektedir.

Anahtar kelimeler: *Antifungal, Candida, identifikasyon, köpek, kromojenik agar*

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Introduction

The oral microbiota of both humans and animals consists of a diverse array of bacteria and yeasts (Willis and Gabaldon, 2020). Dogs, like humans, harbor a variety of yeasts in their oral mucosa, and their colonisation patterns and pathogenic potential require further investigation. Despite the critical role of the oral microbiota in maintaining canine health, research on the isolation and correct identification of yeasts began in the 20th century (Brito et al., 2009). The oral microbiota in dogs is highly diverse and complex, making it challenging to fully characterize. Fungal colonization of the oral cavity in canines is primarily associated with yeasts of the genera *Candida* spp., *Malassezia pachydermatis*, *Trichosporon* spp., *Rhodotorula* spp. and *Geotrichun* spp. with yeasts of the genus *Cryptococcus* being isolated less frequently (Jin and Lin, 2005; Bentubo et al., 2010; Brilhante et al., 2018). The genus *Candida* exhibited a high prevalence, constituting 82.2% of the isolated yeast profile. Notably, *Candida zeylanoides*, a rare species even in humans, was isolated from the oral mucosa of dogs, suggesting that this fungus may represent a new "ecological niche" in canine microbiota, with potential for opportunistic pathogenicity (Navarro et al., 2020).

Out of a total of 100.000 yeast species, approximately 200 are deemed pathogenic, with 50 of them commonly associated with mycoses. Yeasts are responsible for most mycoses in humans and animals, with *Candida*, *Cryptococcus*, *Malassezia*, and *Trichosporon* being the most notable genera (Watkinson et al., 2015). Pathogenic yeasts may induce anorexia and adipsia in animals, leading to compromised immunity and clinical complications (Navarro et al., 2020). Yeasts are symbiotic inhabitants of the canine microbiota, but they can become pathogenic under certain conditions and cause discomfort and pain (Jadhav and Pal, 2006; Brito et al., 2009).

Candida is a fungus that can form pseudo hyphae and reproduce through budding, with a size of 5µ and an oval or round shape depending on its subspecies and environmental conditions. Hippocrates and Galen first described it as an oral lesion in the 4th century BC. In 1839, Bernhard Rudolph Konrad von Langenbeck obtained an organism from the oesophageal mucosa of a patient who had died of typhus and initially thought it was a parasite that caused typhus, which he called "Typhus Leichen" (typhus bodies) (Talay and Odabaş, 2002). Finally, in 1923, Roth Berkhout demonstrated that this organism was not a species of Monilia and proposed that it be named "*Candida*". In the 1800s and early 1900s, there was some confusion and misclassification in naming, but the binomial classification of *Candida albicans* was fully adopted in 1954. Recently, there have been increasing reports of higher incidences of non- *albicans Candida* species mentioned above (Williams and Lewis, 2011). In addition to *C. albicans*, other important species isolated from clinical infections include *C. glabrata*, *C. guilliermondii*, *C. krusei*, *C. lusitaniae*, *C. parapsilosis*, *C. pseudotropicalis*, *C. stellatoidea*, and *C. tropicalis* (Patil et al., 2015). The significant phenotypic variability observed in *Candida* species, and the rise in antifungal resistance among strains, has emerged as a major clinical concern (Navarro et al., 2020).

The prolonged use of antibiotics and a high intake of carbohydrates in the diet may destroy or suppress the competitive bacterial microbiota, disturbing its balance with the host organism and allowing for the excessive growth of yeasts (Lacaz et al., 2002). Senility, likely exacerbated by poor oral hygiene practices in dogs throughout their lifetime and other predisposing factors as mentioned earlier, is considered a significant condition predisposing to periodontal disease. A study involving stray dogs found that animals over 4 years of age were more susceptible to developing this disease, ranging from mild gingivitis to severe periodontitis (Paula et al., 2021).

Early detection of potentially pathogenic yeasts associated with these organisms in the oral microbiota is crucial, as it provides additional clinical assistance for disease diagnosis and treatment (Kurtzman et al., 2011).

The incidence of yeast mycoses has significantly increased, rendering it a significant public health concern, particularly in systemic clinical conditions and hospital-acquired infections. Antifungal medications used in human and veterinary medicine exhibit specific characteristics concerning their chemical structure and mechanism of action, directly or indirectly interfering with the fungal cell and producing fungistatic or fungicidal effects (Paula et al., 2021).

The main classes of antifungal agents used for the treatment of invasive fungal infections include polyene antifungals (such as amphotericin B), azoles (including fluconazole, voriconazole, ketoconazole, itraconazole, and posaconazole), pyrimidines (such as 5-fluorocytosine), and echinocandins (such as caspofungin and micafungin) (Pappas et al., 2009). This study, investigated the presence of *Candida* species in 60 samples of canine oral swabs. The aim of this study was to diagnose the *Candida* species present in the oral flora of dogs and to determine the antifungal susceptibility of these species.

Materials and Methods

Samples

A total of 60 healthy dogs (32 females and 28 males) were randomly selected for the study from a sample of dogs presented to various veterinary clinics in Aydın. Sterile oral swab samples were obtained from different regions of the oral cavity, including the gingival mucosa, dental biofilm, and periodontal sulcus (Santin et al., 2013). The samples were transported under cold chain conditions (+4°C) to the Faculty of Veterinary Medicine Microbiology Laboratory at Aydın Adnan Menderes University for further analysis.

Phenotypic Identification

The oral swab samples were inoculated onto HiCrome™ Candida Differential Agar (Hi-Media, India) for the isolation of *Candida* spp. and incubated at 30°C for 48 hours. Gram staining was performed on the colonies grown on the chromogenic agar, and they were identified as *Candida* spp. based on their size, shape, and

budding characteristics observed in the Gram staining, before being subjected to colony typing. The colonies identified as *Candida* spp. were further identified based on the colour of their colonies on chromogenic agar: *C. albicans*-light green, *C. tropicalis*-metallic blue, *C. glabrata*-cream-white, *C. krusei*-purple, *C. parapsilosis*-light purple, and *C. utilis*-light pink (Brito et al., 2009).

Genotypic Identification

The colonies identified as *Candida* spp. were subcultured onto Sabouraud Dextrose Agar (Hi-Media, India) and incubated at 30°C for 48 hours. DNA was extracted from purified colonies using a MagAttract HMW DNA extraction kit (Qiagen, Netherlands). PCR analyses using ITS3 and ITS4 primers were performed for molecular identification of *Candida* spp. The field strain confirmed as *C. albicans* by Sanger sequencing method was used as positive control and sterile deionized water was used as negative control. For this purpose, Taq Premix (2x) 10 µl, ITS3 (5'-GCATCGATGAAGAACGCAGC-3') and ITS4 (5'-TCCTCCGCTTATTGATATGC-3') primers (100 pmol) 0.2 µl each, $MgCl_2$ (50 mM) 0.5 µl, 5 µl DNA, and ddH_2O were added to a total volume of 20 µl for each sample. For amplification, thermal cycling was performed using thermal cycler with an initial denaturation at 94°C for 4 minutes, followed by 30 cycles of denaturation at 94°C for 30 seconds, annealing at 55°C for 30 seconds, extension at 72°C for 1 minute, and a final extension at 72°C for 4 minutes. Following the PCR analysing, the resulting amplicons were electrophoresed on a 2% agarose gel containing ethidium bromide at 80V for 40 minutes. Bands between 250-500 bp on the gel in the imaging system (Vilber Lourmat, Germany) were considered *Candida* spp. (Fujita et al., 2001).

Antifungal Susceptibility Test

The susceptibility of *Candida* isolates identified phenotypically and genotypically was evaluated using the disk diffusion method. Colonies were inoculated into Brain Heart Infusion Broth (Hi-Media, India) and adjusted to a density of 0.5 MacFarland. The isolates with their densities adjusted were inoculated onto Mueller Hilton Agar No.2 (Hi-Media, India) and the indicated disks were placed, followed by incubation at 30°C for 48 hours (CLSI, 2018). In this study, resistance to three different antifungal groups was investigated, namely the polyene macrolide group, the azole group, and the pyrimidine group. The active substances used were nystatin (100 U) from the polyene macrolide group; ketoconazole (10 µg) and miconazole (10 µg) from the imidazole class of the azole group; fluconazole (10 µg) from the triazole class of the azole group; and flucytosine (1 µg) from the pyrimidine group.

Results

In this study, 60 oral swab samples from dogs were inoculated onto HiCrome™ Candida Differential Agar (Hi-Media, India). The *Candida* colonies were identified based on the colours they produced on chromogenic agar. After incubation, colony growth was observed in 30 (50%) of the petri dishes containing samples taken from female dogs, with colony growth being detected in 17 (53.1%) of these samples, and in 13 (46.4%) of the male dogs' samples. Six different *Candida* species were diagnosed from the 57 colonies obtained. Among the isolated colonies, 16 (28.1%) were purple, 10 (17.5%) were white-cream, 10 (17.5%) were light purple, 9 (15.8%) were light pink, 7 (12.3%) were metallic blue and 5 (8.8%) were light green in colour. The colonies with a purple colour were identified as *C. krusei*, white-cream as *C. glabrata*, light purple as *C. parapisilosis*, light pink as *C. utilis*, metallic blue as *C. tropicalis*, and light green as *C. albicans* (Figure 1).

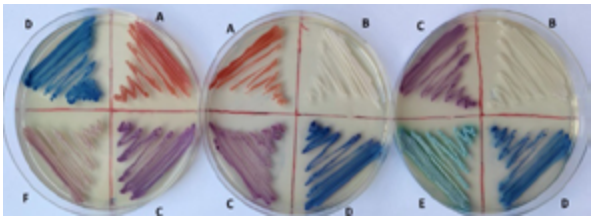

Figure 1. *Candida* colonies colours and morphologies on Candida chromogenic agar.
A. *Candida utilis*; B. *Candida glabrata*; C. *Candida krusei*; D. *Candida tropicalis*; E. *Candida albicans;* F. *Candida parapsilosis*

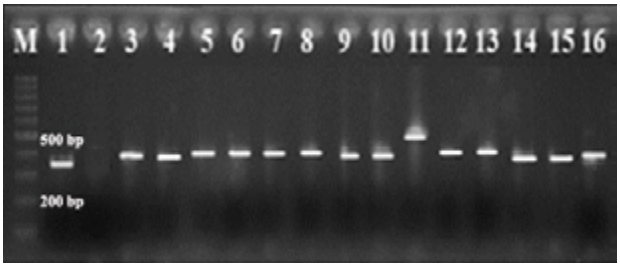

Figure 2. ITS3-ITS4 PCR analysis electrophoresis image of *Candida* species.
M: Marker; 1: Positive control; 2: Negative control; 3-16: *Candida* spp. isolates

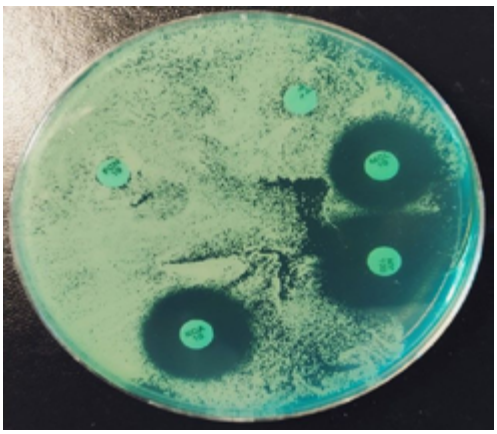

Figure 3. Imagine of the antifungal disk diffusion method performed on Mueller Hinton Agar.
FCN: Flucytosine; FY: Fluconazole; MCL: Miconazole; NY: Nystatin; KCA: Ketoconazole

The growth patterns of *Candida* colonies on chromogenic agar were observed to be either single or multiple. Fourteen petri dishes exhibited growth of a single *Candida* species, 8 petri dishes exhibited growth of two *Candida* species, 5 petri dishes exhibited growth of three *Candida* species, and 3 petri dishes exhibited growth of four *Candida* species (Table 1).

Table 1. Distribution of the isolated *Candida* isolates.

Sample number	Age	Gender	*C. krusei*	*C. parapsilosis*	*C. glabrata*	*C. utilis*	*C. tropicalis*	*C. albicans*
1	2	Female	+		+	+		+
2	2	Female	+		+		+	+
3	2.5	Male	+	+		+	+	
4	2.5	Female	+		+			+
5	2.5	Female		+		+		+
6	2.5	Female	+		+	+		
7	2	Female			+	+	+	
8	2	Male		+	+	+		
9	2	Female	+		+			
10	2.5	Male	+		+			
11	2	Male	+				+	
12	2	Male	+				+	
13	2	Female		+		+		
14	2.5	Male		+		+		
15	2.5	Female	+					+
16	3	Female			+	+		
17	2.5	Female	+					
18	2.5	Female	+					
19	2.5	Male	+					
20	2	Female		+				
21	2	Male		+				
22	2.5	Male		+				
23	2.5	Female		+				
24	2.5	Female		+				
25	2	Female		+				
26	2	Male		+				
27	1.5	Male		+				
28	2	Female					+	
29	2	Male					+	
30	2.5	Male			+			

Fifty-seven Candida isolates were subjected to phenotypic identification, and PCR analyses revealed that all of them produced bands in the 250-500 bp range (Figure 2). Antifungal susceptibility testing was performed on 57 isolates that were genotypically confirmed as *Candida* spp. (Figure 3). It was observed that four isolates identified as *C. krusei* exhibited resistance to all tested antifungal agents. Resistance to the pyrimidine group was detected in 100% of the isolates (n=57). Among the azole antifungal groups, the triazole class demonstrated the highest resistance rate (93.1%), whereas the polyene macrolide group exhibited the highest sensitivity (93.1%). An analysis of antifungal susceptibility based on active compounds revealed that all isolates (n=57) were 100% resistant to flucytosine, while 93.1% (n=53) were resistant to fluconazole, 43.8% (n=25) to miconazole, and 26.3% (n=15) to ketoconazole. In contrast, 93.1% (n=53) of the isolates were susceptible to nystatin. Notably, four isolates resistant to nystatin were identified as *C. krusei*. Additionally, all isolates were determined to have developed resistance to at least two antifungal agents.

Discussion

The present study provides critical insights into the prevalence and antifungal susceptibility of *Candida* species isolated from the oral flora of dogs, with notable implications for both veterinary medicine and public health. The findings highlight the diversity of *Candida* species in canine oral samples, the high prevalence of antifungal resistance, and potential zoonotic risks.

In this study, *C. krusei* (28.1%) was identified as the most prevalent species, contrasting with other studies such as

Navarro et al. (2020), who reported *C. albicans* as the dominant species (39.5%). Interestingly, our findings show *C. albicans* as the least frequent isolate (8.8%), which may be attributable to differences in geographical location, sampling techniques, or the health status of the dogs studied. Furthermore, the distribution of species such as *C. parapsilosis* (17.5%) and *C. tropicalis* (12.3%) aligns with studies by Brito et al. (2009), who reported similar prevalence rates in canine oral samples, though with minor variations. These discrepancies may reflect environmental factors, host-specific microbiota dynamics, or methodological differences between studies.

The detection of antifungal resistance in this study raises significant concerns. Notably, all isolates resisted at least at least two antifungal agents, with 100% resistance observed against flucytosine. This is consistent with findings by Olabode et al. (2016), who reported high flucytosine resistance rates in *Candida* species isolated from dogs. Resistance to fluconazole was also alarmingly high (93.1%), corroborating findings by Brilhante et al. (2015), who documented fluconazole resistance in *C. tropicalis* isolates from animal sources. The high prevalence of fluconazole resistance may be linked to the widespread use of azoles in both human and veterinary medicine, potentially contributing to cross-resistance in *Candida* populations. This underscores the need for judicious use of antifungal agents and implementing antimicrobial stewardship programs in veterinary settings.

Interestingly, *C. krusei* isolates in this study exhibited resistance to all antifungal groups, highlighting their inherent resistance to certain antifungal agents, particularly azoles. This finding is concerning, as *C. krusei* is known for its reduced susceptibility to conventional antifungal treatments (Navarro et al., 2020). The observation that nystatin retained the highest sensitivity (93.1%) among the antifungal agents tested is promising, particularly for managing infections caused by *Candida* species in veterinary practice. Similar findings by Yurayart et al. (2013) reinforce the utility of polyenes like nystatin as effective antifungal agents for resistant *Candida* strains.

The identification of multiple *Candida* species in single samples suggests a complex fungal microbiota within the canine oral cavity. This polymicrobial nature of *Candida* infections has previously been documented by Živković et al. (2013), who found mixed infections in dogs with stomatitis. In our study, 43.3% of the samples exhibited polymicrobial growth, with up to four *Candida* species isolated from a single sample. This diversity has significant clinical implications, as co-infections may contribute to antifungal resistance and complicate treatment strategies.

From a zoonotic perspective, the findings underscore the potential risk of cross-species transmission of resistant *Candida* strains. Dogs, as companion animals, share close physical contact with humans, facilitating the exchange of microorganisms. Previous studies (Kobayashi et al., 2008) have highlighted the potential for zoonotic transmission of *Candida* species, particularly in immunocompromised individuals. In this context, the high prevalence of antifungal resistance observed in this study warrants further investigation into the role of dogs as reservoirs of resistant fungal pathogens.

Despite the comprehensive nature of this study, certain limitations should be acknowledged. The sample size, although sufficient to identify trends, may not fully represent the broader canine population. Additionally, the lack of clinical data on the health status of the dogs limits the ability to correlate *Candida* prevalence and antifungal resistance with specific host factors. Future studies should aim to include larger sample sizes, incorporate detailed clinical histories, and investigate molecular mechanisms underlying antifungal resistance.

Conclusion

In conclusion, this study highlights the diversity and antifungal resistance of *Candida* species in dog's oral flora, with important implications for both veterinary and public health. The high resistance rates observed underscore the urgent need for antimicrobial stewardship and the development of alternative antifungal strategies. Given the close interaction between humans and dogs, the zoonotic potential of resistant Candida strains cannot be ignored. Further research is needed to better understand the dynamics of cross-species fungal transmission and resistance evolution.

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Author contribution statement

Concept: OD, HTYD; Design: OD, HTYD; Data Collection or Processing: OD, HTYD, YS; Analysis or Interpretation: OD, HTYD, SK; Literature Search: OD, HTYD, YS, SK; Writing: OD, HTYD.

Conflict of interest

The authors declare that they have no conflict of interest in this study.

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