



Oral Candidiasis Review: Pathogenesis, Clinical Presentation, And Treatment Strategies

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<p>CC License CC-BY-NC-SA 4.0</p>	<p style="text-align: center;">Abstract</p> <p>The candidiasis is an opportunistic infection commonly affecting the oral cavity. The most prevalent clinical symptoms of candidiasis seen in medical and dental practice is oral candidiasis. People who are extremely young, elderly, or already ill are more likely to develop the illness. The present review summarize classification, pathophysiology, laboratory diagnosis and treatment and management of oral candidiasis. Additionally, medicinal herbs and nutraceuticals can be explored as a safe, accessible, and cost-effective therapy option for oral candidiasis.</p> <p>Keywords: Oral candidiasis, candida albicans, fungi, oral thrush, medicinal plants</p>
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Introduction

The candidiasis is an opportunistic infection commonly affecting the oral cavity (1). Oral candidiasis is one of the most common clinical manifestations of candidiasis encountered in medical and dental practice. Although, oral candidiasis is rarely fatal, it is often associated with local discomfort, altered taste sensation and dysphagia. Thus, it significantly contributes to morbidity and reduction in the quality of life (2,3). Oral candidiasis is the most common human fungal infection especially in early and later life. In the general population, carriage rates have been reported to range from 20% to 75% without any symptoms. More than 20 species of candida, *Candida albicans* are the most common and important causative agent of oral candidiasis (4). *C. albicans* is the only species that can grow in multiple morphological forms that ranges from yeast to pseudohyphae to hyphae. It is more virulent compared to other species (5). It has been reported that oral manifestations caused by candida also differ as per geographic location. Candidial linear gingival erythema is highly reported from developing countries whereas, erythematous candidiasis is more common in developed countries (6). Oral candidiasis has been associated with multiple host risk factors, including impaired salivary gland function, denture wearing, oral mucosa disruption, medication (long-term administration of broad-spectrum antibiotics, corticosteroids, antidepressants, antineoplastic drugs, and immunosuppressant), age (common in neonates and the elderly), endocrine alterations (diabetes mellitus, pregnancy, renal failure, and hyperthyroidism), dietary factors (high-carbohydrate diet and iron-deficiency anemia), cancer, and HIV infection (7-9). Elimination of the predisposing factors is an important strategy in

treating oral candidiasis. The diagnostic approach was focused on both clinical and cytological/histopathological examinations of the oral tissues. In most times, biopsy-based diagnosis helped in confirming clinically identified fungal conditions. In addition, microbial isolation, identification, culture, and antifungal susceptibility provides standard therapeutic care, whereas the organism candida may be cytologically/histological detected in an individual in the absence of a clinical oral condition (10-13). The present review summarizes classification, pathophysiology, laboratory diagnosis and treatment and management of oral candidiasis. There are multiple clinical presentations of oropharyngeal and esophageal candidiasis caused by *C. albicans*, either alone or in mixed infection. Thus, with the above outlook, the present review comprehends the varied clinical manifestations and the current treatment strategies for this opportunistic pathogen.

Methodology

In practice, different tools exist that facilitate literature searches, in addition to visiting a local library and communicating with peers. Using a combination of search terms from the PubMed, Medline databases, Cochrane Library databases, and manual searches on Google Scholar and the bibliographies of identified articles.

Clinical spectrum

Oral candidiasis is classified into pseudomembranous, erythematous, and hyperplastic forms. Candida-related oral lesions include angular cheilitis, denture stomatitis, and central papillary atrophy. Candidiasis has also been linked to leukoplakia, lichen planus, and lupus erythematosus as a super-infection. Oral infections are a secondary site of infection in generalized candidiasis. The clinical appearance of oral candidiasis varies depending on the type.

Pseudomembranous candidiasis

The most common kind of oral candidiasis is pseudomembranous candidiasis, which causes white or yellow scrapable plaques on the oral mucosa. Pseudomembranous candidiasis is a kind of candidiasis that can be acute or chronic. Patients with immunological dysregulation or immunosuppressive medicines are more likely to develop the pseudomembranous form of oral candidiasis (9).

Atrophic Candidiasis

The erythematous condition can be acute or chronic. The mucosa of atrophic candidiasis is diffusely reddened and often relatively dry. The red areas are frequently confined to the mucosa beneath dental appliances such as partial dentures or orthodontic retainers. Atrophic candidiasis affects approximately 26% of patients who wear complete dentures (14). Erythematous candidiasis is frequently seen in people taking corticosteroids or broad-spectrum antibiotics.

Chronic hyperplastic candidiasis

A white plaque on the commissural region of the oral cavity indicates chronic hyperplastic candidiasis. This condition is known as "candidal leukoplakia." The white plaque areas in chronic hyperplastic candidiasis are difficult to remove. Hyperplastic candidiasis can last for years without causing any symptoms (15).

Denture Stomatitis

It is also known as "chronic atrophic candidiasis." As the name implies, it is linked to candidiasis, which is normally asymptomatic but can cause pain in the denture-bearing area. Denture abnormalities serve as a breeding ground for candida and other bacterial pathogens. The acidic and anaerobic environment in the denture's tissue surface promotes yeast development. Denture-related candidiasis is characterised by diffuse erythema and edoema of the denture bearing area and is frequently linked with angular cheilitis in clinical terms (16).

Median Rhomboid Glossitis

It appears on the tongue as a symmetrical chronic lesion anterior to the circumvallate papillae. Atrophic filiform papillae make up the structure. Median rhomboid glossitis is a diamond shaped, elevated, inflammatory lesion of the tongue, covered by smooth red mucosa. An erythematous or white-erythematous region on the dorsal median surface of the tongue, right prior to Region V of the circumvallate papilla, is the

most prevalent clinical presentation of the condition (terminal gingiva) (7). A biopsy of this location reveals the presence of candida in more than 85 percent of cases. It's frequently linked to cigarette smoking and the usage of inhaled steroids (9).

Angular cheilitis

The commissural regions of angular cheilitis are characterised by erythematous fissuring. Angular cheilitis is a type of cheilitis that affects the It's an erythematous fissure at one or both corners of the mouth that's frequently caused by a candida infection inside the mouth. Staphylococci and streptococci have also been implicated. Facial wrinkling near the corners of the mouth and along the nasolabial fold, particularly in the elderly, creates a continuously moist environment that predisposes to this lesion. (7) In long-term denture users, this wrinkling is exacerbated by resorption of the alveolar ridges, which results in a decrease in the height of the lower face when the mouth is closed. Deficiency of iron and vitamin B12 are also implicated in the etiology of this condition.

Chronic Mucocutaneous Candidiasis

It refers to a category of unusual diseases in which recurrent mucocutaneous candidiasis responds poorly to topical antifungal treatment, and which may contain a diagnosable immunological deficiency.

Pathogenesis

Candida albicans is the predominant causal organism of most types of candidiasis. Almost half of the population is infected by this relatively harmless organism. *Candida parapsilosis*, *Candida krusei*, *Candida stellatoidea*, *Candida tropicalis*, *Candida glabrata*, *Candida guilliermondii*, and *Candida dubliniensis* are some of the other species seen in oral candidiasis lesions. Other species, including *C. krusei*, have been noticed in immunocompromised individuals. *C. glabrata* is a new cause of oropharyngeal candidiasis in patients undergoing radiation therapy for head and neck cancer (17). In patients with HIV infection, new species, such as *Candida dubliniensis* and *Candida inconspicua*, have been recognized. Oral candidiasis has been cited as another important risk factor associated with diabetes. Oral candida carriage in diabetic patients is influenced by a number of variables, including xerostomia, decreased chemotaxis, phagocytosis failure, and salivary pH abnormality. Oral candida was found to be more common in diabetic individuals than in non-diabetic patients, according to Mohammadi et al. (2016) (18). Antibiotics, anti-cancer, immunosuppressive, and anti-cholinergic drugs have been linked to oral candidiasis due to changes in the oral microbial flora, which normally inhibits candidal growth (19). Candida infections occur as a result of changes in the host defense system, in which both immunological and non-immunological factors play important roles in creating conditions favourable for candida proliferation (20). Table 1 details the various predisposing factors that are involved in the development of many of the clinical forms of oral candidiasis.

Table 1: The various predisposing factors

Local predisposing factors	Systemic predisposing factors
Impaired local defense mechanisms	Impaired systemic defense mechanisms
Reduced saliva secretion	Endocrine disorders including diabetics, hypothyroidism and hyperthyroidism
Epithelial changes and atrophic oral mucosal diseases (e.g. oral lichen planus)	Rheumatic disease
Altered or immature oral flora	Nutritional deficiencies (iron and folate)
High carbohydrate diet	Immunosuppressive conditions such as chemotherapy, deficiencies of humoral or cell mediated immunity, HIV/AIDS
Denture wearing	drugs as broad spectrum antibiotics, corticosteroid and contraceptive pills, chemotherapy.
Topical medications e.g. corticosteroids	Some congenital conditions
Decreased blood supply (e.g. caused by radiotherapy or vasculitis)	
Poor oral hygiene, Smoking	

Laboratory diagnosis of oral candidiasis

Correct diagnosis allows for specific treatment of a fungal infection, which may prove lifesaving or prevent complications from occurring. Oral candidiasis is diagnosed primarily clinically, based on the professional's recognition of lesions, which can be confirmed by microscopic identification of candida (21). Exfoliative cytology, imprint specimen for microbiology culture, potassium peroxide staining, oral swab specimen for culture analysis, salivary assays, and oral mucosal biopsy are all diagnostic methods for oral candidiasis.

Microbiological diagnosis can be confirmed by taking oral swabs. oral swabs are subjected to KOH mount, Gram staining followed by isolation on SDA (Sabouraud Dextrose Agar). Species identification of candida is done by Germ tube test, growth on CHROM agar, assimilation and fermentation of sugars and lastly antifungal susceptibility testing is done for therapeutic use (22).

Commercial systems: Rapid commercial system (Microstix- Candida and oricult-N) for diagnosis of oral candidiasis is useful for identification where microbiological laboratories are not within the access (23). Some other techniques like Morpho typing, resis to typing and serotyping are basically used for strain differentiation and epidemiological studies of candida and candidiasis (24).

Molecular methods like species-specific PCR approaches have also been used for Candida species identification. Candida based on genetic variation are analyses of electrophoretic karyotype differences and restriction fragment length polymorphisms (RFLPs) using gel electrophoresis or DNA-DNA hybridization

Serological tests: Serological tests are frequently used to ascertain the clinical significance of Candida species isolates. Rising titers of IgG antibodies to *C. albicans* may reflect invasive candidiasis in immunocompetent. Tests like enzyme linked immunosorbent assay (ELISA) and radioimmuno assay (RIA) for detection of candidial antigen.

Immunodiagnosis: The use of specific antibodies labelled with fluorescent stain permits causative organisms to be diagnosed accurately within minutes. (25) In definitive diagnosis, special staining procedures such as periodic acid–Schiff are useful to identify and quantify.

In chronic hyperplastic candidiasis, an oral mucosal biopsy procedure is recommended to distinguish it from leukoplakia and assess the status of dysplasia (26). The etiologic factors must be taken into account when making a diagnosis. Bacterial and viral infections, as well as immune pathologic diseases, must all be considered, especially if antifungal treatment is ineffective.

Treatment and management of oral candidiasis

The treatment of oral candidiasis is based on early and accurate diagnosis of the type of oral candidiasis, correction of predisposing factors or underlying diseases, and use of appropriate antifungal medications. Controlling predisposing or facilitating factors, as well as promoting good oral hygiene and periodic oral examination, are critical to preventing infection and facilitating treatment if it occurs. An empiric form of anti-candidiasis treatment is sometimes used to treat people who have a localised burning sensation in their mouth. Because laboratory tests for candidiasis are so expensive, most clinicians treat oral candidiasis on an empirical basis. The culture methods aid in quantifying candidiasis organisms as well as distinguishing between normal and elevated levels of oral candidal infections (9). The patient's immune status, the specific characteristics of oral candidiasis like clinical presentation, aetiology, susceptibility to antifungal drugs, organic location, dissemination, and the pharmacological properties of the available antifungal drugs should all be considered when selecting an antifungal drug. (27) Generally recommended antifungal agents are depicted in the table 2. These drugs target fungal infections by altering RNA or DNA metabolism or causing intracellular peroxidation. The Infectious Diseases Society of America (IDSA) revised its clinical practise guidelines for the treatment of candidiasis, including oral candidiasis, in 2016 (28). Treatment of mild disease with miconazole is one of the recommendations (muco-adhesive buccal 50-mg tablet once daily for 7-14 days). Nystatin suspension (100,000 U/mL, 4-6 mL, four times daily) or pastilles are alternatives for mild disease (1-2 pastilles, 200,000 U each, four times daily for 7-14 days). Furthermore, the World Health Organization stated that topical nystatin suspension or pastilles can be used instead of oral fluconazole to treat oropharyngeal candidiasis in HIV-positive children and adults (29). Mostly the infection is simply and effectively treated with topical application of antifungal ointments. However, in chronic mucocutaneous candidiasis with immunosuppression, topical agents may not be effective. In such instances systemic administration of medication is required. Oral application of probiotics can serve as an adjuvant in treating oral candidiasis (30). Probiotics such as *Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* LC705, *Propioni bacterium freudenreichii*, and *shermanii* JS were used in a recent study. The use of probiotic cheese reduced the prevalence of oral candida in the elderly, as well as the prevalence of hyposalivation (31).

Patients undergoing cancer treatment with fluconazole are less likely to develop oral candidiasis than those receiving topical polyenes. It was found that patients undergoing bone marrow transplants who were given a chlorhexidine rinse as a prophylaxis were very successful. Antifungal prophylaxis given daily or weekly reduces the incidence of oral candidiasis in chemotherapy and radiotherapy patients, as well as in HIV patients, with a decrement in recurrent oral candidiasis (7).

Table 2: Antifungal medications

Medication	Formulation/Dose	Indication
Nystatin	Suspension 60 ml/4-6ml/6hr Ointment 30gm/ 2-4 application Tablet/day every 8 hr	Intraoral candidiasis, Angular cheilitis
Anphotericin B	50 mg for infusion/ 100-200mg/6hr	Intraoral candidiasis, chronic erythematous candidiasis, Denture stomatitis
Clotrimazole	Gel /cream 1%/3 times/day Tablet /troches 10mg/5times/day	Angular cheilitis Intraoral candidiasis
Miconazole	Gel / cream 100mg/6hr	Angular cheilitis, chronic erythematous candidiasis
Ketoconazole	Gel 2%/3 times/day Tablet/200mg 1-2/day	Angular cheilitis Pseudomembranous candidiasis, acute Erythematous candidiasis, chronic hyperplastic candidiasis
Fluconazole	Tablet/50-100mg/day Suspension/10mg/ml	Pseudomembranous candidiasis, acute erythematous candidiasis, chronic hyperplastic candidiasis Oropharyngeal Candidiasis
Itraconazole	Capsule/100-200mg/day	Pseudomembranous candidiasis, acute Erythematous candidiasis, chronic hyperplastic candidiasis
Betamethasone dipropionate clotrimazole	Cream/4 times/day	Chronic angular Cheilitis
Voriconazole	Infusion First day: 6 mg/kg once every 12 h Rest of the treatment: 4 mg/kg once every 12 h First day: 200–400 mg once every 12 h Tablet/Rest of the treatment: 100–200 mg once every 12 h	Intraoral candidiasis
Posaconazole	Oral suspension/Tablet First week: 200 mg, 4 times/day Rest of the treatment: 400 mg, 2 times/day	Oropharyngeal Candidiasis

Natural products as alternative promising anti-candida drugs

The search for therapeutic applications of medicinal plants and their derivatives has grown in the past years throughout the world. Several studies have been carried out in order to evaluate new biological properties from the biodiversity. For many years a wide variety of natural products have traditionally been used as antifungal agents, especially those of the genus *Candida*. Considering that oral candidiasis is a frequent opportunistic infection mainly caused by *Candida* colonization, the use of these substances may play an important role in the management of oral candidiasis. Table 3 Several plant species showed effective anti-candidal activities.

Table 3: Natural anti-candida Drugs

Plant	Common name	<i>Candida</i> species	MIC ($\mu\text{g/mL}$)	Reference
<i>A. squamosa</i>	Sugar apple or custard apple	<i>C. albicans</i>	Methanol and chloroform extracts: 600 and aqueous extract: 800	32
<i>Funtumia elastica</i>	Silk rubber	<i>C. albicans</i>	100,000	33
<i>C. nucifera</i>	Coconut	<i>C. glabrata</i>	25% (1:4 dilution)	34

		C. tropicalis C. parapsilosis C. stellatoidea C. krusei C. albicans		
C. leptospadix	Dhangri bet or Rab bet	C. albicans	60	35
A. sieberi	Wormwood	C. glabrata	37.4-4781.3	36
A. minus	Wild rhubarb or lesser burdock	C. albicans C. dubliniensis C. glabrata C. krusei C. stellatoidea C. tropicalis	12,500 12,500 25,000	37
A. campestris	Field wormwood	C. glabrata C. lusitaniae C. tropicalis C. krusei C. parapsilosis	25,000 50,000	38
A. frigida	Fringed sagebrush or pasture sage	C. parapsilosis C. lusitaniae C. krusei C. tropicalis C. glabrata	50,000 12,500 6000 400	38
S. gigantea	Tall goldenrod or Giant goldenrod	C. tropicalis C. lusitaniae C. albicans C. krusei C. glabrata	12,500 1600 800 100	38
A. biebersteinii	Yarrow	C. albicans	100,000	39
A. viridis	Green alder	C. albicans C. glabrata C. parapsilosis C. krusei C. lusitaniae	12,500 25,000 200 6000	38
B. alleghaniensis	Yellow birch	C. parapsilosis C. albicans C. krusei C. lusitaniae C. glabrata	3000 800 400 50	38
B. tomentosa	Tanibuca	C. albicans C. tropicalis C. krusei C. glabrata C. parapsilosis C. dubliniensis	200-12,500	40
T. bellirica	Myrobalan or beach almond	C. albicans	1-3	41
C. papaya	Papaya	C. albicans	250	42
S. zenkeri	Divida	C. guilliermondii C. parapsilosis C. tropicalis C. glabrata C. krusei C. lusitaniae C. albicans	6250 4680 3900 2340	43
M. obtusifolia	Golden bellbean	C. albicans	Pomolic acid: 12.5-25 Plant extract: 160-320 Ursolic acid:	44

			50-100 2-epi-tormentic acid: 50-100	
<i>P. venusta</i>	Flame vine	<i>C. krusei</i> ATCC 6258 <i>C. krusei</i> USP 2223 <i>C. albicans</i> ATCC 10231 <i>C. albicans</i> USP <i>C. albicans</i> of <i>C.</i> <i>parapsilosis</i> USP <i>C. tropicalis</i> USP <i>C. guilliermondii</i> USP	Crude extract: 3-24	45
<i>C. dentata</i>	Assegai tree	<i>C. albicans</i>	Leaf extract: 111 Stem bark extract: 610	46
<i>C. colocynthis</i>	Bitter apple or bitter cucumber	<i>C. albicans</i> <i>C. glabrata</i> <i>C. krusei</i> <i>C. parapsilosis</i> <i>C. guilliermondii</i> <i>C. tropicalis</i> <i>C. dubliniensis</i>	3125-12,500	47
<i>D. crassiflora</i>	Gabon ebony	<i>C. glabrata</i> <i>C. albicans</i> <i>C. krusei</i> <i>C. tropicalis</i>	25,000 12,500	48
<i>L. spiralis</i>	Leiothrix	<i>C. albicans</i> <i>C. krusei</i> <i>C. parapsilosis</i> <i>C. tropicalis</i>	62.5 15.7 15.7 31.25	49
<i>D. ecastaphyllum</i>	Red propolis	<i>C. albicans</i> ATCC 76645 <i>C. albicans</i> LMP-20 <i>C. tropicalis</i>	25	50
<i>T. tetraptera</i>	Prekese	<i>C. glabrata</i> <i>C. krusei</i> <i>C. tropicalis</i> <i>C. albicans</i> <i>C. guilliermondii</i> <i>C. lusitaniae</i> <i>C. parapsilosis</i>	6250 3120	51
<i>A. myriophylla</i>	Albizia	<i>C. albicans</i> <i>C. glabrata</i> <i>C. guilliermondii</i> <i>C. krusei</i> <i>C. parapsilosis</i> <i>C. tropicalis</i>	100-400	52
<i>G. glabra</i>	Licorice	<i>C. albicans</i> <i>C. glabrata</i> <i>C. parapsilosis</i> <i>C. tropicali</i>	187.5 1500	53
<i>C. alata</i>	Senna	<i>C. albicans</i>	26900	54
<i>C. erythraea</i>	Common centaury	<i>C. albicans</i>	100	55
<i>C. pulchellum</i>	Lesser centaury	<i>C. albicans</i>	400	55
<i>C. spicatum</i>	Spiked	<i>C. albicans</i>	200	55

	centaury			
C. tenuiflorum	Slender centaury	C. albicans	200	55
P. graveolens	Rose geranium	C. tropicalis	125	56
R. uva-crispa	European gooseberry	C. lipolytica	4630	57
		C. glabrata	4600	
R. nigrum	Black currant	C. tropicalis	7160	57
		C. guilliermondii	6130	
		C. inconspicua	4220	
		C. parapsilosis	4410	

Conclusion:

Oral candidiasis is one of the most prevalent opportunistic fungal diseases of the oral cavity that affects humans. The prognosis for oral candidiasis is good when proper treatment is given and predisposing factors associated with this illness are eliminated. When systemic predisposing variables are present, the chances of candidiasis recurrence increase. Oral candidiasis is frequently caused by a secondary superficial infection that can be treated with antifungal medication and proper oral hygiene. In order to avoid oral candidiasis, medicinal plants and nutraceuticals can be explored as a safe, accessible, and economical management alternative.

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