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REVIEW ARTICLE

Candidiasis Types, Causative Agents, and Treatment Methods

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ARTICLE INFORMATIONS

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ABSTRACT

Objectives: This review aimed to spotlight an important fungal infection called candidiasis caused by candida, explaining the main type of candidiasis and the species considered a causative pathogen agent with the study of the treatment methods**.**

Conclusion: Candidiasis is a common yeast infection, and the species *Candida albicans* is most prevalent, *candida* is normal flora in the skin, mouth, and vagina, and can transfer to the pathogen causing candidiasis in immunocompromised Patients and is mainly treated by using of synthetic antifungal and sometimes medicine plant used in treatment successfully.

INTRODUCTION

One of the most common fungal infections is candidiasis caused by many Candida species*; Candida* is found normally in the skin and inside the body cavities such as the mouth, throat, gut, and vagina, without causing infection. *Candida* can cause infections if it grows out of control, especially in immunocompromised Patients, or enters the bloodstream or internal body organs. About 200 species of candida were identified, 15 species of them classified as pathogenic agents for human, and *C. albicans* is the most prevalent species in Candida infection.[1] The most common types of candidiasis are vaginitis, oral candidiasis, cutaneous candidiasis, candidemia, and systemic infections.[2]

Type of Candidiasis

- *Oral Candidiasis (Thrash):* This infection affects the mucosal layer of the mouth cavity and is considered a common fungal infection in humans.[3,4]
  Some time oral candidiasis developed into oropharyngeal candidiasis especially in a patient with cancer or AIDS and another immune-compromised disease. Oropharyngeal candidiasis including many cases, for example, acute atrophic, acute pseudomembranous, chronic atrophic, chronic hyper-plastic, angular cheilitis, and rhomboid glossitis.[5]
- Vulvovaginal candidiasis is the second most common reason of vaginitis; 75% of all women will get vulvo-vaginal candidiais in their lifetime, and mostly in pregnant women.[6]
- Cutaneous candidiasis: This infection usually affects intertriginous and interdigital areas, especially in fat people. The clinical symptoms of infection are characterized by dry, erythematous, erosive, scaly skin and pustules.
  Candida can affected skin and nails, causing candidal folliculitis, chronic mucocutaneous candidiasis, diaper candidiasis, and onychomycosis.[7]
- *Systemic candidiasis:* Affects deep body organs like heart, spleen, liver, kidney, and brain or by the entry of candida in bloodstream; example for systemic candidiasis are candidemia, a form of blood sepsis (fungemia),

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invasive candidiasis, chronic systemic candidiasis and (hepatosplenic candidiasis).[8]

Causative Pathogen Agents

There are many species of *Candida* consider a causative agent of different types of candidiasis *C. tropicalis, C glabrata, C pseudotropicalis, C guillierimondii, C krusei, C lusitaniae, C parapsilosis, C stellatoidea. C albicans* and *C glabrata.*

The more frequent species in candidiasis are:

C. albicans

A polymorphic yeast can be found in either yeast form state that is a non-invasive or fungal form the invasive phase, sugar fermenting organism. The common shape of the colony is creamy or white color smooth colonies with a distinctive yeast odor on SDA medium. On the differential candida medium CHROM agar candida the colony appeared as glistening green, *C. albicans* formed a thick wall structure called chlamydospore when grown on corn meal agar. When *C. albicans* is incubated for 3 hours in human serum at 30°C, Germ tubes will appear as long tube projections extending from the candidal cells. The carbohydrate assimilation was positive for the same sugers like dextrose, sucrose, trehalose and xylose, and negative for lactose, reffinose, and others. The carbohydrate fermentation test showed positive test for dextrose, galactose, and trehalose and a negative for lactose and sucrose.[9]

C. glabrata

Originally, C. glabrata was classified in the Torulopsis genus due to its lack of pseudohyphae. In fact, in 1978, this species was shown to have no polymorphic growing, being grown as blastoconidia.[10]

C. glabrata cells are smaller than *C. albicans C. tropicalis*, and *C. parapsilosis* blastoconidia.[11] Regarding the differential candida medium CHROMagar Candida *C. glabrata* colonies appear either white or pink to purple color depending to the biochemical reactions, it ferments only glucose or trehalose.[10]

C. glabrata also common cause of candidiasis after *C. albicans. C. glabrata.*[12] The treatment of *C. glabrata* infections is very difficult, so that the mortality rate high in compromised and at-risk hospitalized patients. This yeast is often resistant to many azole antifungals especially fluconazole and many azole antifungal agents.[13]

Genetically *C. glabrata* is distinguished from *C. albicans* by its small-subunit rRNA.[14]

C. tropicalis

Candida tropicalis most important pathogenic Candida species with high virulence. It is distinguished from *C. albicans* and *C. dubliniensis* by producing true hyphae, the character of producing true hyphae exclusive of *C. tropicalis* also has a strong ability to biofilm production and can adhere to epithelial membranes.[15]

C. tropicalis formed dark blue colonies on CHROM agar Candida Figure 1 Macromorphological identification of C. tropicalis appear with Cream and smooth colonies when incubated for 2 days at 30oC on SDA medium while the

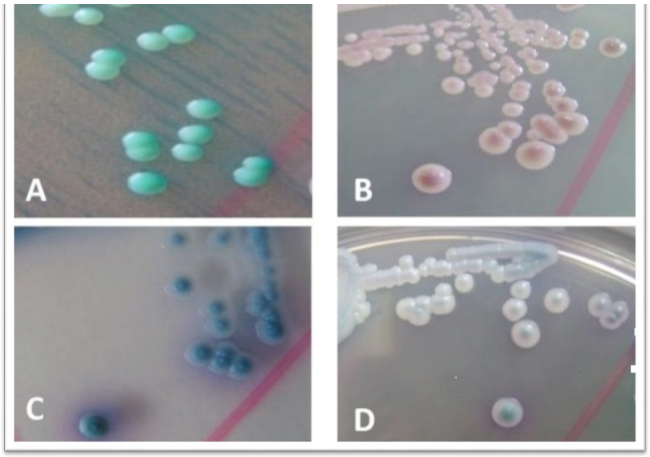

Figure 1: The color of candida spp in CHROMagar Candida medium: (A) Green color *C. albicans*, **(B)** Pink color *C. glabrata*, (C, D) Blue or blue gray *C. tropicalis*.

colonies color in candida differential medium CHROM agar Candida is the dark blue color after 4day of incubation at 35°C. *C. tropicalis* produced single or chains blastoconidia, also true hyphae and pseudohyphae produced after incubation in YPD medium containing 20% bovine serum for one week at 30°C.[16]

Treatment of Candidiasis

There are two ways for treated candidiasis

Use of Antifungals

Antifungal is the medicines (natural or synthetic compound) that used to treat fungal infection.

There are many similarities between fungal and mammalian cells because they have a similar structure, metabolic activity, and many complex life processes so that the antifungal drug will break down the cells of fungal pathogen and affect the cells of the cells host. The main chemical differences between fungal and host cells are that fungal cells have a cell wall, while human cells do not possess, and Ergosterol considers the main compound of fungal cell membrane, but Cholesterol is substituted in human cell membranes.[17]

Main antifungal groups

Azole Group

It is the largest group of antifungal drugs that inhibit ergosterol biosynthesis via inhibiting Cytochrome P450, which converts lanosterol to ergosterol.[18]

The Azole groups are used to treat candidiasis, systemic candidiasis infections and skin fungal infection Dermatomycosis.[19]

This group include Fluconazole, itraconazole and clotrimazole, Fluocazole was more active in treating candidiasis and other fungal infections during the early years of its discovery, but over-used led to increased fungal resistance.[20]

Echinocandins Group

The antifungal of this group inhibits the synthesis of the main substrate of the fungal cell wall (B-1, 3- glucan) by inhibiting B-1, 3-D, glucansynthase enzyme. this group includes

Micafungn, Caspofungin which is used in the treatment of different cases of candidiasis, specially candidemia.[21]

Polyenes Group

This group binds with ergosterol in fungal cell membrane resulting in increased permeability so that the fungal cell will lose important contents, especially K ions, and destroy. The antifungal of the polyene group is less toxic than other antifungal because the mode of action of this groupe stracted in destroying ergosterol, which is found only in fungal cells while mammalian host cells contain cholesterol. The common antifungal of this group is Nystatin used to treat oral candidiasis and amphotericin B, which treated cases with systemic candidiasis.[22]

Allylamines Group:

This antifungals group inhibit ergosterol biosynthesis in the fungal cell wall by obstructions of Squalene epoxidase, the important enzyme in ergosterol biosynthesis.[23]

Recently, four antifungal rancids have been approved by a United States Food and Drug Administration FDA department. This rancid included echinocandin, azole, amphotericin B, and Flucytosine.[24]

Many *Candida* spp acquired resistance toward these antifungals so that the treatment will be insufficient, at last time, many plant extracts were used successfully in the inhibition of the candidal growth in vitro and in vivo to avoid resistance toward antifungal and these extracted plant compounds do not possess any undesirable side effects.

Use of Plant Extracts

The use of medicinal plants nowadays has become widespread over the world. The plants have common side effects, so that the treatment with medical plants became more popular worldwide. There is an increasing need for safe and effective novel compounds for treatment. Many active compounds extracted from plants are known for their medicinal properties, including antifungal activity. Ethanol extracts of Lawsania inermis (Henna), Portulaca oleracea (Baq'lah) promising drugs use successfully against C. albicans and bacteria.[25]

Ethanol extracts of *Cassia siamea, Odina wodier, Momordica charantia*, *Syzygium jambolanum* and *Melia azedarach* have significant inhibitory activity against candida isolates. The concentration 100 mg/mL for *Syzygium jambolanum* extracts recorded high antifungal activity while *Sargassum wightii* ethanolic extract was active at 10 mg/mL.[26]

Astronium sp. Extracts have antifungal activity, especially *A. urundeuva* leaves extract succeeded in controlling the growth of two major etiological agents of candidiasis (*C. albicans* and *C. glabrata*).[27]

The Rosmarinus officinalis extract was tested against the prevalent species of Candida (*C. albicans*), and the result showed good antifungal activity of these plant extracts.[28]

Mimosa caesalpiniifolia that belong to Leguminosae family consider promising prospective antimicrobial compounds, the leaf extract of this plant contain about 28 compounds that are identified as antifungal drugs. Phytochemical study permitted the identification of many novel flavonoid compounds of apigenine such as, 8-(β -oliopyranosyl)apigenin (1), 6-(β-boivino-pyranosyl)apigenin (2), 7, 5″-anhydro-6-(α-2, 6-dideox- hydroxyarabino-hexopyranosyl) apigenin (3) and (E)-6-(2- carboxyethenyl) apigenin (4). The chemical structure of these novel compounds was determined successfully by using spectroscopic analysis techniques. Compound (4) showed high antifungal activity against C. krusei, resistant to azoles group antifungal. Also, an association of some identified novel compounds was active to reduced inhibition concentration value more than 100-fold.[29]

In vivo study of phenolic plant, compounds were achieved by studied fractions activity of Larrea divaricata Cav. The aqueous extract shows improved production of the superoxide anion with increasing the phagocytosis process of *C. albicans* and improves the nitric oxide (NO) production compared with control treatments. So that the actin of extracts not only on macrophage activation but also have an important role represented by production and releasing of ROS and NO, which contribute to the pathogens' injury.[30]

Syngonanthus nitens, Euphorbia hirta L, *Centellaasiatica*, *Cymbopogoncitratus* (DC) *Stapf* (Gramineae), *Areca* Cathechu, L. *Piper* Betle L., *Terminaliacatappa* extracts have an active role in slowing the progressive vulvovaginal candidiasis.[31]

Alcoholic extracts of some plants like, *Fagonia indica* (Shoka'a), *Avicennia marina* (Qurm), *Portulaca oleracea* (Baq'lah), Lawsonia inermis (Henna), Asphodelus tenuifolius (Kufer), Ziziphus spina-christi (Sidr) have high activity against C. albicans. Both Henna and Baq'lah extracts exhibited high potent activity against candida with recording of 10 µg/mL MIC. Furthermore, able to inhibit biofilm formation and age resistance of C. albicans in active growth phases.[32]

Three types of dates from Oman are described to possess strong activities against *candida*.[33] The activities of date seeds are due to the occurrence of phenolic compounds, such as p-coumaric, ferulic and sinapic acids, flavonoids, and procyanidins.[34]

Syzygium samarangense leaf extract was studied against *C. albicans*, *C. krusei*, *C. parapsilosis, C. glabrata, C. auris,* and *C. tropicalis* and gave significant antifungal activity. The MIC of the extract was (100–125) mg/mL. fungal morphology analysis using scanning electron microscope showed cell wall degradation of *C. albicans* when treated with studying extract. The viability of C. albicans decreased 75 percent when infected skin was treated with Syzygium samarangense leaf extracts.[35]

CONCLUSIONS

Candida an opportunistic yeast cause infection in immune-compromised patients in different parts of the body called candidiasis, and this infection can be treated by topical or systemic antifungal like nystatin and amphotericin B.

But in some cases, *candida* acquired resistance to antifungals and becomes useless, so that the plant extracts are a very promising medicine.

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