



A Review on Candidiasis resistance current drug development process in its prevention and treatment

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ABSTRACT

A fungal infection caused by *Candida albicans* leads to illness and death worldwide. This review mainly focused upon Vulvovaginal Candidiasis that is a common fungal infection seen in women, especially during pregnancy; *Candida* species cause diseases, particularly in immunocompromised patients. This type of infection occurred during the nonsterile environment. The different types of candidiasis mentioned in this review are Mucosal Candidiasis, Oropharyngeal Candidiasis, Vulvovaginal Candidiasis, Cutaneous Candidiasis, Invasive Candidiasis, Disseminated candidiasis, and Candidemia. New approaches like vaccination, antibodies, cytokine therapy, amphotericin-B loaded nanofiber, mucoadhesive are required to improve the result of the patients suffering from infections. New insights into the mechanism of anti-candidal host response have contributed to the design of novel immunotherapy. The systemic and topical treatment is carried. The novel drug therapy is given in order to avoid the resistivity developed by fungus. Diagnosis is made by different techniques like direct examination and Culture Method. The other examination methods used are Pathogen-related tests, mannan tests, nucleic acid-based assays. Amphotericin-B loaded nanofibers and liposomes are developed and even certain plant extracts are using as an antifungal drug which is safer to use the future trends used for the study are Echinocandins, the latest class of drug used for the antifungal and drug act as a fungicidal that has low drug-drug interaction which makes first-line treatment for invasive candidiasis particularly. The different class of drugs has been used for the treatment are discussed with Azoles that are used in the treatment with a combination of the other class drugs.



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INTRODUCTION

Candidiasis and *Candida* resistance

Candidiasis

In nowadays, the fungal infection is gradually increased, and it is registered as one of the important threats to the patients. In worldwide Candidiasis caused by *Candida albicans* is a main fungal infection which is infected by *Candida* species, and this leads to the illness and death of human being. *Candida albicans* is a class of symbiotic, pathogenic organism, *Candida albicans* effect at an early stage and which mainly affect the mucosal

surfaces, mainly the skin, GIT along with oral cavity and urinary tract. Oropharyngeal Candidiasis is one of the frequent oral indications of HIV infection. Vaginal Candidiasis target a significant number of women during their pregnancy. Oropharyngeal Candidiasis is one of the frequent oral indication of HIV infection and which is commonly founded in neck and head cancer patients, for these patients is treated by corticosteroids and antibiotics (Thompson *et al.*, 2010).

Candida resistance

Use of more range of drug for the treatment of antifungal therapy this leads to the development of resistance by the microorganism, For example, azole is a primary drug for the treatment of anti-fungal therapy this act by blocking the production of lanosterol, but this microorganism develops a secondary mechanism to develop the resistance against the drug. In the case of echinocandins, it acts by blocking 1,3- β -D-glucan. It is a component of cell wall synthesis, but the organism develops the secondary mechanism and develops the resistance; to overcome this, developing a novel drug delivery with combining both the drug is used, which increases the activity of the drug (Balkis *et al.*, 2002).

Etiology

The Candida species they can found both in the skin and ecological may be in exogenous and endogenous that are mentioned below in the Figure 1 and it is commonly isolated organisms from the bloodstream of a patient

MATERIALS AND METHODS

Most important types of Candidiasis are

Mucosal Candidiasis

These types of infection are limited to the non-sterile membrane surface, for instance, the bodily cavity and also vaginal fungal infection. *Candida albicans* is the class with the highest occurrence among human yeast isolates and is the major opportunistic yeast pathogen is mainly in warm-blooded animals. Candida species are often found in the hospital, walls, food, air, and other surfaces. Additionally, Candida can be seen on the body of hospital staff, and nosocomial multiply among patients has been traced to employees' carriage (Vazquez and Sobel, 2002).

Oropharyngeal Candidiasis (OPC)

Oropharyngeal Candidiasis is the more frequent infection in patients infect human HIV and is prognostic of progressive immunosuppressant. Oral ketoconazole management is usually successful,

although the return is common.

Vulvovaginal Candidiasis

Vaginal Candidiasis is found to be more frequent and trickier to eliminate during childbearing; however, no current studies have been carried out, and the original studies suffered methodological flaws. Sporadic and recurrent is another name of Vulvovaginal Candidiasis. This is given based on the episodic frequency, the pathogen of both infection, and to formulate unique disease management, and it is very difficult to differentiate between sporadic and recurrent (Sobel *et al.*, 1998).

Cutaneous Candidiasis

Cutaneous mycosis (CCC) presents inside the primary half dozen days of life as an exanthema caused by Candida species. Cutaneous Candidiasis is a very common infect which affect the human beings within the lifetime 100 cases in 300 people were reported as Candida infection. This cutaneous Candidiasis is usually affecting the skin and nail for the patients. It is chronic or also subacute infections. The cutaneous disease is generalized or localized to the skin and nails (Mahmoudabadi, 2006).

Invasive Candidiasis

Invasive Candidiasis is one of the main cause for the death of hospitalized patients, current treatment for invasive Candidiasis include fluconazole, amphotericin B, voriconazole, caspofungin (Pappas and Evalua, 2006). During the treatment of invasive Candidiasis, echinocandins are using as the most important drug & it is also the safest drug profile. Invasive infections have the ability to affect all the organs, invasive fungal infections mainly affected by *c.albicans*, in recent time disease, is gradually increased because of non-albicans Candida species and antifungal resistance.

Disseminated candidiasis

For the patients who are suffering from systemic Candida, they require intensive care; this infection is increased gradually. In the past 5 years, as a result, a combination of factors, the patients who are suffering immune suppression from anti-neoplastic and also anti-rejection chemotherapy and the patients are admitted to the ICU (Vincent *et al.*, 1998). The organ invasive and systemic hematogenous disseminated is a severe case of Candidiasis, which spread the Candia cell into the body and this has the capacity to affect the important organs and causes the failure of the organ this leads to the death of the patients to avoid this intensive antifungal therapy is given (Pappas *et al.*, 2003).

Candidemia or (bloodstream infections) BSI

From the last ten years, the Candida infection is isolated from the bloodstream of hospitalized patients has gradually increased, and species linked with this infection as changed. The Candida patient they are at high risk, and they are admitted in critical care unit in the hospital. In conditions like acute leukemia, burns, leucopenia, and premature birth predisposal patients, the treatment is given with multiple antibiotics, prior Hickman catheterization and organisms are isolated from blood and hemodialysis is done. In addition, the various investigation is done on nosocomial candidemia at the University of Iowa Hospitals, and clinics are reviewed. Due to the increase in cost and duration of treatment, Candida species are the 4th leading cause of hospital-acquired BSIs, reaching 8 to 10% of all BSIs acquired in hospitals.

Novel immunotherapeutic strategies

By using novel immunotherapeutic, we can fight against the pathogens, and the current strategies used are vaccination, antibodies, and Cytokine therapy (Veerdonk et al., 2010). In Figure 2, it is mentioned.

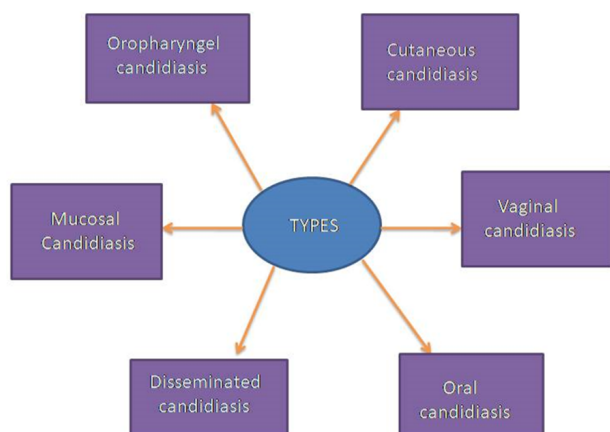


Figure 1: Types of Candidiasis have been noted on the basis of the place where it occurs

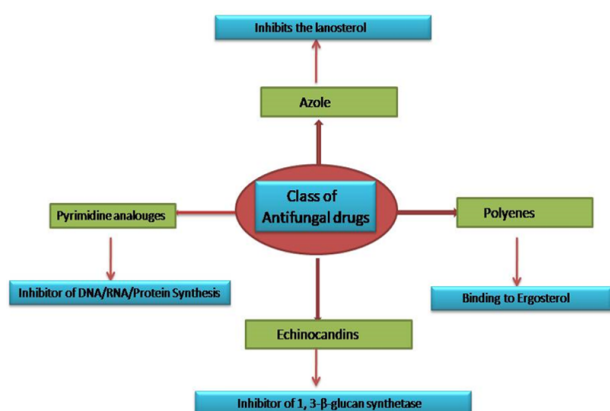


Figure 2: The different class of anti-fungal drugs shown above with their mechanism of action

Vaccination

The vaccine therapy for the Candida infection is still in the preliminary stage; presently, hardly few Candida vaccines are available in clinical, some of the vaccines like active and passive fungal vaccine shown to be promising to be a safety and effective strategy. The vaccine is prepared by using sorbitol as inactive excipients; then, this is mixed with active components like MPG_KP and ribosomes, then fill it in a capsule. Currently, vaccine formulations can be improved by using adjuvants like dectin-2, D-glucan, which are particularly against pathogens (Levy et al., 1989).

Antibodies

Antibody treatment is also one of the important therapy for treatment against candidiasis, and patients with monilia disease human recombinant antibody are targeted against the Hsp90 it is a pathogen-specific heat protein and study is developed by using 140 patients who are affected by invasive candidiasis the study name is double-blinded randomized multicentric study (Matthews, 1992). Both animal models and humans were used for preliminary screening, and this shows promising results.

Cytokine therapy

This cytokine has the capability to defend the host, and this acts as an immuno-modulation for the infection. GM-CSF, by using the myeloid cell (it is a blood cell that is formed from a progenitor, a cell for the granulocyte or platelets) this increases the rate of hematopoiesis this leads to the formation of neutrophils (Gadish et al., 1991). The purest form of human GM-CSF is prepared by using supernatant liquid of mitogen this produce fresh human T-cell which is obtained from endogen, USA, Boston and this is transferred at conc. of 10000 units ml-I and this is kept in an agar for fermentation in soft agar gel where one unit of GM-CSF number of colonies was increased in double. This cytokine therapy has proven to be the best novel drug therapy for treating patients of advanced malignancies. The purpose of this therapy is to increase the immune response in the body to fight against the infection (Richardson et al., 1992).

Amphotericin-B loaded poly nanofibers

Vulvovaginal candidiasis is an inflammation that is mainly localized in the vulvovaginal area. The treatment is systemic and local administration of anti-fungal drugs, but this can be failed because of resistance developed by the Candida class species, and the other one is noncompliance by the patients. To avoid this Amphotericin B-loaded poly nanofibers

(lactic-co-glycolic acid) are used signally, and this is also one of the controlled drug delivery systems, and this is also one of the alternative therapy for local treatment of vaginal Candidiasis. These nanofibers acted as a controlled drug release and delayed the release of drug-like amphotericin-B for more than 8 days; this gives us a good in vitro anti-fungal activity and this act against the vaginal fungus infection after 3 days of continuous treatment. In vitro drug release of Amphotericin-B from PLGA nanofibers: Nanofibers physical and chemical properties are analyzed by analytical techniques and by using in vitro drug delivery and study by this we can analyze the drug release and the in vitro and in vivo activity of fungicidal of drug release from nanofibers was determined by using the agar diffusion method (Halperin *et al.*, 2016).

RESULTS AND DISCUSSION

Mucoadhesive

Fluconazole loaded oral strips for local treatment of oral candidiasis

Mucoadhesive is prepared by using fluconazole as a loaded drug, and it is intended for buccal mucoadhesive oral strip for treatment of oral mycosis, this mucoadhesive oral strip was prepared by using solvent casting technique by using various compound mixture (Rençber *et al.*, 2019). Oral disease is mainly caused by excess growth of fungus species particularly the oral moniliasis (OC) which mainly affect the oral and oral candidiasis is one of the major risk factors in human due to its immunological disorder, hyposalivation (this result in the reduction of salivary flow rate) this can be cured by medication or by radiotherapy and chemotherapy and other is oral flora this is mainly caused because of excess growth of monilia Albicans (Aksungur *et al.*, 2004). In the early stage of the oral candidiasis fluconazole is given at 100 mg per day for up to 1 to 2 weeks for both the case of immune-compromised patients and immune-competent patients, with this other drug-like triazole is also given to enhance the activity of drug, this fluconazole block the production of ergosterol which is important element in fungal cell wall. The administration of fluconazole through the oral result in the alternation in GIT leads to vomiting, abdominal discomfort, and bloating. This also causes irritation and serious hepatotoxicity. By using solvent Castin method mucoadhesive oral strips were prepared, for this EUD RS-100, EUD RL-100, HPMC K100M, and HPMC E50 are used as a polymer which is a very specific and sensitive polymer, and it is also a safe one to use and which is also helpful for the controlled release of the drug (Vasan-

tha *et al.*, 2011).

Plant extracts for Candidiasis

In recent years the candidiasis incidence and other fungal infections have been gradually increased, particularly for the immune-compromised host. One the possible approach of curing is by using medicinal plants like anti fungal chemotherapeutic substances the different drugs used have been mentioned in Table 1, (Cohen *et al.*, 1981).

For the treatment of infection in Unani and ayurvedic physicians, they referred to different products of medical plants in treating jaundice, cough, viral infection, fungal infection, wounds, and skin diseases. The mechanism of action of anti-Candida natural products by blocking the growth and biofilm formation and also inhibit the cell metabolism, cell membrane plasticity (Shaltout, 2004).

Resistance developed to plant product

In some cases, natural products show resistance against unciriatomentosa. This is because of the increased capacity of Candida to form a bio film. Are listed inTable 1 ('Plants' natural products as alternative promising anti-Candida drugs. PDF, no date)

Toxicity of natural anticandidal product

Usage of amphotericin B and fluconazole at 5µg/ml shows 10% of cell lysis, whereas in geraniol oil at 5µg/ml, it shows 1% of cell lysis, this shows that the geraniol oil is safer to use. M.royoc extract is also nontoxic according to the American national cancer institute, and also oral administration of this drug shows less toxic effect, this shows that M.royoc is a very good anticandidal drug

Diagnosis

Candida albicans are generally identified by a phenotypic method, which includes testing of their morphological features, the examination of their ability to ferment different carbohydrate substrate, and the ability to assimilate nitrogen compounds (Johnson, 2009).

Direct Examination

The microscopic examination is a rapid method, and it is very cost-effective for the identification of candidiasis. It involves scraping or swabbing the affected area, followed by placing the swab on the microscopic slide. Further, a 10% KOH solution is added in order to dissolve the skin cells without affecting the integrity of the Candida cells. This allows complete visualization of pseudohyphae as well as the budding yeast cells, which correspond to various Candida species (Hani *et al.*, 2015). In

Table 1: List of anti-Candida Albicans natural products reviewed: origins, Zone of collect, used Part(s) and experiment

Plant	Zone of collection	Part used	product	Experimental
Abutilon theophrasti	Korea	Aerial parts	Hibicuslide C fraction of methanol extract	Invitro
Acacia nilotica	India	leaves	Crude ethanolic extracts	Invitro
Acacia nilotica	India	Bark	Essential oil	Invitro
Aloe vera	India	Leaves	Ethanol extract	Invitro
Alpinia conchigera	Malaysia	Dried and ground pseudostems and rhizomes	Methanol extract	Invitro
Carica papaya	India	Leaves and seeds	Hydro ethanol extract	Invitro
Coriandrum sativum	Brazil	Aerial fresh part, dried material	Essential oil, hexane extract(HE)	Invitro

case of disseminated mycosis, microscopic examination of component of fungi is done by wet and glued mounts adding of components like calcofluor white this allows fast identification of fungi part by bind to polysaccharide in the cell wall of fungi and on excitation by UV rays, then specimens are colored by acid Schiff or gomoris urex silver stains (Gauglitz *et al.*, 2012).

Culture Method

The most frequently used media for Candida species is dextrose agar media; these media allow the growth of Candida and suppresses the growth of some other bacteria due to the low pH. In this method rubbing of a sterile swab to the affected place then agar medium and placed it for incubation at 37°C for 2 days for proper development of colonies on the basis of characterization, biochemical characterization, physiological of colony specification of Candida is done (Ilkit and Guzel, 2011). A range of differential media available for Candida speciation includes Pagano-Levin agar, Nickerson s medium phosphomolybdate agar and chromogenic medium Chromogenic media (CandidalD, CHROM agar, Candi select 4 and Candida media) are also implied for speedy identification of Candida Chromogenic substrates present in these media react with yeast cells by enzymes secreted to give particular colony characteristic and pigmentations which are species-specific and thus allow easy speciation (Horvath *et al.*, 2003).

Examination of stained specimens

Gram stain

Gram stain usually stains yeast in purple, and this helps to separate from the bacterial cell. The gram stain would not stain the yeast cells evenly. Index 40X magnification, the yeast cells are viewed as circular or oval-shaped and sometimes with buds. When observed with oil immersion, they are visualized in the form of giant gram + cocci. Few yeast-like organisms usually develop rectangle-shaped arthroconidia through true hyphae (Fenn, 2007).

Calcofluor white

C-Albicans is the frequent reason for infections, occurred by organisms like yeast. Another group of organisms like Torulopsis (Candida) glabrata, are ever more significant, predominantly in immunocompromised individuals. Calcofluor white stain fluorescence under filtered ultraviolet light to enhance the binding to the cell wall, mainly the polysaccharides in chitin this view as a bright green color (Harrington and Williams, 2007).

Pathogen-related tests

β -D Glucan Detection Method

The fungal species cell wall is mainly made up of 1-3 beta-D-glucan as a structural element; this is a polyose that is not found in the rest of organisms like viruses or mammals, whereas this polyose present within the systemic circulation of patients has been particularly used as an indicator of invasive candidiasis. This is an essay used to detect BDG has been developed, this helps for the activation of natural process pathway that found in amoebocyte lysates of the Japanese horseshoe crab, Tachypleustridentalis (Ellepola and Morrison, 2005).

Mannan test

Cand-tec latex agglutination test is very sensitive, and specificity among various tests. The potential in detecting the infection is very limited in the identification of *Candida* species (Lass-Flörl and Mayr, 2009). The double sandwich enzyme immune assay plateia *Candida* antigen has been reported as more sensitive. The mannan test we do the mutual testing of antigen and anti-body both; this allows improving diagnosis with is more effective than compared to antigen testing alone.

The specificity and sensitivity of this test is around 80 to 85%, according to diagnostic and management guideline for fungus diseases 2012 suggested that due to its high negative prognosticative worth need to mix of protein and matter testing for designation of candidemia. However, some of the fungi were not detected by this assay like fungus parapsicosis, and fungus guillier has known difungemias (Cuenca-Estrella et al., 2012).

Nucleic acid-based assays

These assay is a convectional mycological diagnosis that gives a fast and sensitive result. Molecular biology techniques like hybridization PCR based techniques or microassay provide rapid detection of *Candida* and *Aspergillus* species for a various clinical specimen. For this method, DNA is amplified by the iso or non-iso thermal method (Posch et al., 2017).

Future trends

Echinocandins are the latest class of a drug for the anti fungal, and this drug act as a fungicidal and is active against bio film production. In addition to this, echinocandins have low drug-drug interaction; this makes echinocandins a first-line treatment for invasive candidiasis, particularly. This acts by blocking the production of 1, 3- β -D-glucan, which is a very important element of the cell wall in fungus. In early days caspofungin was the first drug to get approved by the food and drug administration (FDA) in 2001. Antifungal resistance is one of the major threats for patients and doctors. Fungi develop a secondary mechanism to the currently available antifungal drug. Current resistance in the anti-fungal drug include azole resistance in non-*Candida Albicans* isolate; *aspergillus fumigates* block the azole class of drug and *c.glabrata* block the echinocandins. To avoid this, novel drug delivery has been developed by combining both azole and echinocandins (Murray et al., 2014).

CONCLUSION

Candidiasis treatment is very challenging in therapeutic because of various species are responsible for

the infection, this pathogen they have the ability to penetrate the skin and cause inflammation, burning and redness in the affected skin. There are various antifungal agents which having unique mechanism to block the activity of candidiasis, for example azoles and echinocandins are major class of antifungal agents, but *Candida* species develop resistance against the antifungal drug to avoid this novel drug delivery is using by combining both drugs this help in reducing the resistance. To improve clinical efficacy, new approaches are developed like nanoparticulate drug delivery, liposome, microparticulate drug delivery is developed. In the novel, drug delivery adoptive transfer of prime immune cells, vaccination, antibodies, and photodynamic therapy is developed, which is currently using which is also tested and passed in the clinical and pre-clinical phase, and this could be a future for treatment for *Candida* class species.

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