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Responding to the Hitch in Fighting *Candida Albicans* Through Nanomedicine

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Abstract *Candida albicans, as an opportunistic pathogen has been closely associated with both mucosal and deep tissue life-threatening infections in patients being immunocompromised or hospitalized for some grave underlying ailment. Antifungal therapy so far has not been much successful to reduce mortality and morbidity associated with candidiasis. Furthermore the complete eradication of fungal infection requires long-term treatment that may continue for a month, making patients more vulnerable to adverse effects. The emergence of Candida albicans resistant strains against commonly prescribed antifungals is also a major area of concern demanding immediate consideration. Researchers are continuously investigating newer approaches to counter the deficiencies in conventional treatment strategies. One of these approaches involves the use of nanotechnology to overcome challenges associated with antifungal therapy. This review focuses on various means that have been employed to effectively counter puzzles supplementary to Candida albicans by use of nanomedicines.*

Key Words: Nanomedicine, Candida Albicans, Antifungal Therapy, Long-term Treatment, Drug Resistance

Introduction

One of the most common fungal pathogen of human is *Candida albicans*. Normally it is harmless and commensal organism but it plays the role of opportunist pathogen in case of immunocompromised and immunologically weak patients [1]. *Candida albicans* pathogen is the domain of elaborative research because of its remarkable resistant features and multiple growth forms, i.e. unicellular yeast, pseudohyphal and hyphal forms [2]. *Candida albicans* pathogenic strength and morphogenesis account for its ability to form biofilms. Formation of biofilms starts when yeast cells get attached to the solid support and develop a denser layer of cells [3]. Cells packed in denser layer possess different morphological characters [4]. As far as in vivo properties of biofilms are concerned, they act as a protective agent against host defensive mechanism for *Candida albicans* [5]. Due to increased severity and complications candida infections are considered as fourth most common in the list of hospital-acquired infections and the second most leading cause of death worldwide[6]. *Candida albicans* causes mucosal candidiasis (symptomatic mucosal membrane infections) as well as disseminated candidiasis (candidemia) [2].Commonly existing mucosal membrane infection is pseudomembranous candidiasis (thrush) [2].Thrush is determined by white spots, which readily gets removed after intervals to show inflammatory areas beneath the membrane [7]. Neonates, immunocompromised and topical corticosteroids receiving patients are probably more susceptible to thrush. Mucosal infections of *Candida albicans* majorly attack upon esophageal, oral pharyngeal, gastrointestinal mucosa and vaginal

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membranes [8]. Oral pharyngeal and esophageal mucosal candidiasis are common in immunocompromised patients and resulting in failure to produce saliva [9]. Oral pharyngeal candidiasis is commonly linked with oral cancers and is marker indicator of the AIDS. Vulvovaginal candidiasis (VVC) is a common infection that may affect up to 75% women [10]. Patients taking reproductive hormones, antibiotics and oral contraceptives as well as diabetics are prone to vulvovaginal candidiasis [6]. Over stimulation and expression of inflammatory response is responsible for symptoms of vulvovaginal candidiasis [11].*Candida albicans* bloodstream infections are termed as candidemia. Candidemia infections prevail by residing and colonizing the internal organs [12]. Patients suffering from neutrophils deficiency due to blood cancers and immunosuppressant therapy are susceptible to candidemia. Miscellaneous risk factors include surgery and use of catheters during surgery. Biofilms discussed above are responsible for residing and replicating in the inner walls IV catheters thus spreading *Candia albicans* infectious cells continuously in the bloodstream of the patients[13]

Resistance Mechanism of *CANDIDA Albicans* and Antifungal Therapy

Candida albicans infections have got much virulence and strength due to its overwhelming resistance mechanism such as biofilms formation and activation of efflux pumps [14]. These resistance mechanisms are leading cause of ineffectual antifungal therapy [15]. Moreover prevalent treatment approaches for fungal infections are restricted. Antifungal drug resistance is increasing threshold of invasive *Candida albicans* infection [16]. Moreover it is also leading towards difficult, expensive and even impossible treatment of *Candida albicans*. Current antifungal agents are limited and consist of only following drug classes. Amphotericin B is polyene macrolide and commonly used in the treatment of *Candida albicans* infections [17]. It acts by binding to the fungal cell membrane (ergosterol) and develops pores in the membrane and allows leakage of electrolytes thus causing cell death. Toxicity of Amphotericin B leads to Fever/chills, hypotension, nephrotoxicity, hypokalemia, hypomagnesemia and thrombocytopenia. Nystatin is also a polyene macrolide and its mechanism of action is similar to Amphotericin B most commonly used in the treatment of oral candidiasis (thrush) and vulvovaginal candidiasis (VVC) [18]. Nystatin is too toxic for systemic use [19]. Fluconazole, ketoconazole, itraconazole and miconazole belongs to the azole group of antifungal drugs. Azoles are used to treat all types of candidal infections by inhibiting fungal cell membrane synthesis. Toxic effects regarding azoles are gynecomastia, liver dysfunction, and fever. Flucytosine is a pyrimidine antimetabolite and is used in the treatment of *Candida albicans* systemic fungal infections in combination with Amphotericin B. It acts by inhibiting nucleic acid synthesis of the fungal cell wall. Toxic levels of flucytosine lead to bone marrow suppression

Figure 1: Antifungal Agents and their Mechanism of Action

Nanomedicine as a new Approach to Bypass Antifungal Resistance

As discussed above, *Candida albicans* have developed strong resistance against conventional as well as modern antifungal drugs. Nanomedicines can overcome the drug resistance mechanisms, related to decreased absorption, increased drug efflux from microbial cells, biofilm formation of *Candida albicans* [20]. Nanomedicine aimed at delivering the maximum dose of antifungal agents specifically at the site of infection, thus succeeding in bypassing drug resistance with less adverse effects on the patient.[21]

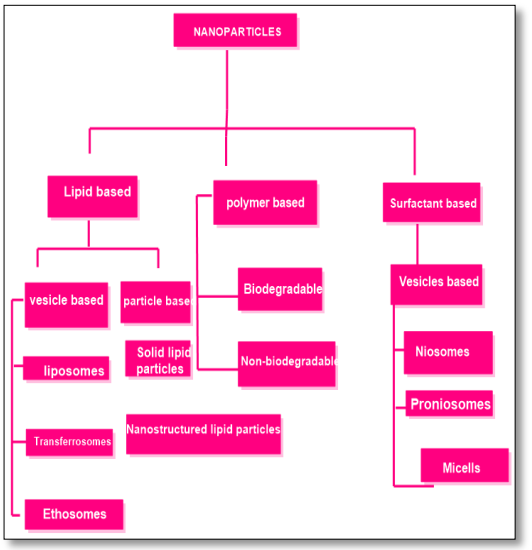


Figure 2: Classification of Systems of Nanoparticles

Lipid-based Nanoparticles

Lipid-based nanoparticles include nano lipid gels, liposomes, ethosomes and solid lipid nanoparticles.

Solid lipid nanoparticles

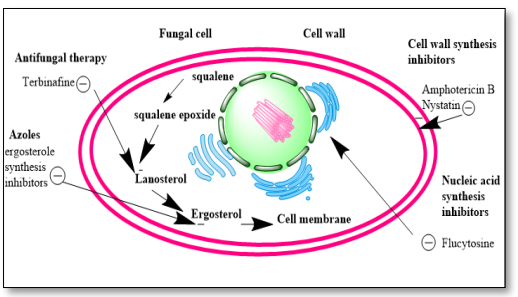
Solid lipid nanoparticles belong to the new class of colloidal drugs. Lipid-based nanoparticles replaced liquid lipid with a solid lipid. Solid lipid nanoparticles are a hallmark in combating antifungal resistance. Various antifungal drugs have been checked with different solid lipid nanoparticles [22]. The most common example, in this case, is of itraconazole loaded solid lipid nanoparticles. Itraconazole loaded solid lipid nanoparticles are effective in the treatment of mucosal candidiasis. Mucosal candidiasis requires increased permeation, moisture content and encapsulation efficiency and all of these parameters are characteristic features of solid lipid nanoparticles [16].

Mucoadhesive nano lipid gel

Fluconazole gel carrying nanolipids as carriers can be synthesized by the phase inversion temperature technique [23]. The gel is used to treat vulvovaginal candidiasis and can be proved as an adequate substitute to the existing conventional antifungal formulations. Moreover fluconazole nano lipid gel is non-irritant, feasible and effective enough to be used for vaginal application because of its moderate mucoadhesiveness and rheological properties [24]. Fluconazole was released in a sustained manner from the nanolipid gel.

Ethosomes

Ethosomes open new era for nano targeted drug delivery
deep inside the skin and systemic circulation.



Ethosomes

bypass various other drug delivery systems because of their safety, stability, efficacy, and simplicity in preparation [25] Ehtosomes have the ability to encapsulate various lipophilic antifungal drugs. Most common and effective antifungal loaded ethosomes is topical fluconazole encapsulated ethosomes. Fluconazole encapsulated ethosomes are formed by incorporating into the appropriate dermatologically tested base and then optimization by the hot method. Researchers found that fluconazole encapsulated ethosomes resulted in a marked decrease in candidiasis lesion size as compared to marketed similar products [26].

Transferosomes

Transferosomes are sophisticated nanoformulations which possess the ability to endure stress with high adaptability. Structurally they are very soft, elastic and deformed vesicular formulations having an inner aqueous core and outer complex lipid bilayer [23]. Owing to the ultra elastic nature of transferosomes they are able to squeeze through the skin pores of very small size [18]. Transferosomes are highly effective in treating candidiasis by overcoming its resistance mechanism and solving the permeability issue of miconazole by synthesizing transferosomes loaded miconazole via thin film hydration technique [27]. Transferosomes are also able to encapsulate poorly soluble antifungal drug fluconazole for achieving prolonged Transdermal drug delivery [28]. Nystatin loaded transdermal transferosomes are also very effective in treating candidemia.

Liposomes

Liposomes are spherical vesicle comprising of lipid layers and consisting framework of phospholipids [29]. Liposomes are best for encapsulating different antifungal drugs and it is an effective vehicle for various anti-fungal formulations [17]. Most commonly used and effective antifungal liposomal preparation is Amphotericin B loaded liposomal formulations. Amphotericin B side effects can be minimized and its activity can be enhanced if it can be formulated in liposomal forms [30]. Liposomal Amphotericin B is effective against the resistance mechanisms of *Candida albicans* in severe candidemia by eradicating biofilms formation in the catheter flow [31]. Liposomal Amphotericin B treats *Candida albicans* infection and eliminates biofilms in a dose-dependent manner [32]. Similarly micoazole is a commonly used antifungal but it is ineffective in treating deep mucosal infections and has some toxicity issues. Flexible liposomes encapsulating miconazole were reported to be effective in treating deep rooted *Candida albicans* infections [33].

Dendrimers

Structure of dendrimers is composed of various polymeric components like core, dendrons and

surface active groups. Dendrimers possess such unique features that the drug can be incorporated in their internal structure or physically linked on their surface. There is only a little research on the antifungal activity enhancement due to Dendrimers [34] Dendrimers are effective in killing *Candida albicans* cells by causing morphological changes in the fungal cell wall and disrupting its mechanism of resistance i.e. biofilms formation. Most useful antifungal loaded dendrimers are polyamidoamine loaded clotrimazole dendrimers and these are active against different resistant species of *Candida albicans* [8]

Metallic Nanoparticles

Metallic nanoparticles aimed at killing *Candida albicans* resistance strains by overcoming resistance mechanism of biofilms formation [35]. Most common and useful metallic nanoparticles against Candida albicans are silver and zinc oxide. The microwave-assisted technique was followed for synthesizing and achieving fast heating and reaction completion of silver nanoparticles. Advancement in nanomedicine resulted in revealing effectiveness and broad-spectrum activity of silver nanoparticles as a bactericidal, virucidal and fungicidal [4]. Silver nanoparticles are found to be highly active against *Candida albicans* by disrupting, creating pores as well as allowing leakage of essential materials, and apoptosis [36]. Most important and remarkable feature of the silver nanoparticles is against the virulent and resistant characters of *Candia albicans* i.e. morphological transformations and biofilms formation. ZnO nanoparticles were synthesized via sol-gel method by using precursors like zinc acetate dehydrate and silver nitrate and very effective against Candida albicans resistant strains by generating reacting oxygen species [37]

Surfactant-based Nanoparticles

Surfactant-based nanoparticles are basically aimed at the skin site because they have the ability to reversibly disrupt the major barrier of the skin i.e. stratum corneum. Most commonly used surfactants based nanoparticles in the treatment of Candida albicans infections are niosomes and micelles

Micelles

Micelles are a mixture of hydrophilic head and hydrophobic tail and comprise of the increased amount of surfactants. Micelles approach is highly encouraging in reducing the cost-effectiveness and toxicity of various antifungal drugs. A most important example is of biodegradable functional polycarbonate micelles for controlled release of Amphotericin B. Amphotericin B is a poor soluble antifungal agent after encapsulation into polymeric polycarbonate micelles resulted in increased bioavailability, cost-effectiveness, solubility, and safety. Amphotericin B encapsulated micelles are highly recommended for treating candidemia infections [38].

Niosomes

Niosomes are composed of non-ionic surfactant and cholesterol. Nystatin is a polyene antifungal drug. It is widely used in the treatment of *Candida albicans* infections but its main disadvantage is its minimal absorption and decreased oral and topical bioavailability. Therefore researchers preferred its administration in liposomal or liposomal form. But nystatin loaded liposomes were not successful as they lack the ability to reach deeper mucosal layers of the skin, less stable and hence also lack systemic effect. Nystatin loaded niosomal transdermal gel possess the ability to overcome all side effects. The formulation was developed by following film hydration technique. Niosomal nystatin formulations are highly stable and sustained resulting in increased bioavailability [39]

Proniosomes

Proniosomes are highly stable and dry surfactant based nanoparticles containing water-soluble carrier coated with surfactants. But their activity is shown when they are rehydrated in aqueous media within minutes. Proniosomes are an excellent strategy for encapsulating drugs to prolong their residence time in systemic circulation [29]. Proniosomes possess penetration enhancers which enhance penetration and targeted delivery of drugs deep into the tissues along with minimized toxicity and cost. Similarly, miconazole loaded proniosomal gel is of significant importance in treating *Candida albicans* infections. Miconazole alone has permeability issues which can be overcome when it gets encapsulated by proniosomes. Miconazole loaded proniosomes have significantly higher activity against *Candida albicans* because of increased permeation of drug through the fungal cell wall and causing inhibition of ergosterol due to the presence of penetration enhancers [40].

Polymeric Nanoparticles

Polymeric nanoparticles are colloidal dispersions having a size less than 1μm and are capable to encapsulate the drug [36] Polymeric nanoparticles are used in the treatment of *Candida albicans* after

encapsulating itraconazole via simple film hydration method. Itraconazole encapsulated polymeric nanoparticles are biocompatible, less toxic, release the drug in a sustained manner and possess the property of inhibiting *Candida albicans* infections and damaging their mechanism of biofilms formation [41] Another important example is the natamycin loaded biodegradable polymeric nanoparticles for treating *Candida albicans* infections more effectively. Natamycin loaded biodegradable were developed by precipitation method and found to be highly permeable, stable, non-toxic and effective.

Carbon Nanotubes

Antifungal activity for *Candida albicans* infection is an interesting and promising field of research and it's attracting new eras
of nanomedicine for alternative treatment options regarding developed resistance mechanism of antifungals. The most novel approach in nanomedicine for treating *Candida albicans* infections is the use of carbon nanotubes and silica magnetic nanoparticles. For achieving better treatment against candida species, scientists tried their best to formulate Amphotericin B conjugated with carbon nanotubes and obtained results were marvelous and marked a reduction in biofilms production was observed[42]

Conclusion

Candida albicans has been of great interest for the scientists because of its pathogenic nature, morphogenesis and ever-increasing mechanism of resistance. *Candida albicans* is a commensal pathogen and is causing severe mucosal as well as systemic infections in immunocompromised patients. All conventional antifungal agents have developed resistance against *Candida albicans* due to its strong resistance mechanism of biofilms formation. Moreover, antifungal therapy is also associated with various risk factors and toxicity issues. Nanomedicine opens a new era of research and development for overcoming all the barriers regarding conventional drug therapy. Nanomedicine involves the use of various categories and compositions of lipid-based nanoparticles, surfactant based nanoparticles, metal-based nanoparticles, dendrimers and carbon nanotubes to treat severe *Candida albicans* infections. Nanomedicine proved to be effective and efficient in combating the resistance mechanism of biofilms formation, toxicity and permeation issues to combat lethal *Candida albicans* infections. It is obvious from the literature that nanomedicines emerged as a successful and effective therapy against *Candida albicans* infections.

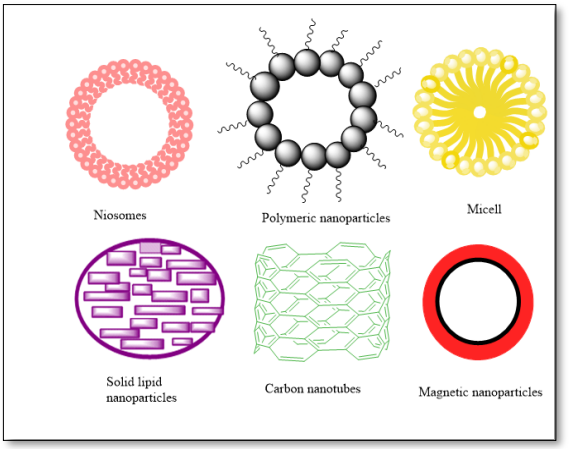


Figure 3: Structure of Nanoparticles used in the Treatment of *Candida Albicans* Infections

References

Joon, K. (2011).Candida albicans: A major human pathogen. The Journal of Microbiology,

Yuvraj, S. D. (2010). Kamta Prasad Namdeo, Oral Candidiasis: A Review. International Journal of Pharmacy and Pharmaceutical Sciences,

Donlan, R. M., (2002). Biofilms: Microbial Life on Surfaces. *Emerging Infectious Diseases, 8*(9), p. 881-890.

Pfaller, M. A., & Diekema, D. J. (2007). Epidemiology of Invasive Candidiasis: a Persistent Public Health Problem. *Clinical Microbiology Reviews, 20*(1), 133-163.

Sahnoun, Z. K., & Jamoussi, (1998). [Free radicals and antioxidants: physiology, human pathology and therapeutic aspects (part II)]. Therapie, 53(4), 315-39.

Dovnik, A., et al., (2015). Treatment of vulvovaginal candidiasis: a review of the literature. Acta Dermatovenerol Alp Pannonica Adriat, 2015. 24(1): p. 5-7.

Jenkins, V., & Postlewaite, J. (1951). Coccidioidal meningitis: report of four cases with necropsy findings in three cases. Annals of internal medicine, 1951. *35*(5), p. 1068-1084.

Webber, M. A., & Piddock, L. J. V. (2003). The importance of efflux pumps in bacterial antibiotic resistance. *Journal of Antimicrobial Chemotherapy, 51*(1), p. 9-11.

Touitou, E., et al., (2000). Ethosomes — novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. *Journal of Controlled Release, 65*(3), 403-418.

Pandit, J. M., Garg, & Jain, N. K. (2014). Miconazole nitrate bearing ultraflexible liposomes for the treatment of fungal infection. *Journal of Liposome Research, 24*(2), 163-169.

Mittal, A. K., Chisti, Y., & Banerjee, U. C. (2013). Synthesis of metallic nanoparticles using plant extracts. *Biotechnology Advances, 31*(2), 346-356.

Ling, X., et al., (2015). Synthesis and characterization of hyaluronic acid-platinum(iv) nanoconjugate with enhanced antitumor response and reduced adverse effects. *RSC Advances, 5*(99), p. 81668-81681.

Haghighi, F. Farahbakhsh, S.R.M., Eskandari, M. (2015). Evaluation of antifungal activity of ZnO/Ag nanoparticles on Candida albicans biofilm.

Ying Wang, P. L. R. (2016). Biodegradable functional polycarbonate micells for Controlled release of amphotericin B. Acta Biomaterialia,

Teemu, J. N. P. K. (1998). Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. *Clinical Pharmacology & Therapeutics, 63*(3), 332-341.

Viswanad, L. T. (2012). Formulation and optimization of clotrimazole - loaded proniosomal gel. Scientia Pharmaceutica,

Müller, R. H., Radtke, M., & Wissing, S. A. (2002). Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv Drug Deliv Rev, 54*, S131-S155.

Galloway, J. W., Keijser, B. J., & Williams, D. M. (2016). *S*aliva in studies of epidemiology of human disease: the UK B iobank project. *Periodontology 2000, 70*(1), p. 184-195.

Webber, M. A., & Piddock, L. J. V. (2003). *The importance of efflux pumps in bacterial antibiotic resistance. Journal of Antimicrobial Chemotherapy, 51*(1), 9-11.

Zotchev, S. B. (2003*).* Polyene macrolide antibiotics and their applications in human therapy. *Curr Med Chem, 10*(3), 211-23.

Rhoads, J. L. et al., (1987). Chronic vaginal candidiasis in women with human immunodeficiency virus infection. *JAMA, 257*(22), 3105-3107.

Joshi, M., & Patravale, V. (2008). *Nanostructured lipid carrier (NLC) based gel of celecoxib. International Journal of Pharmaceutics, 346*(1), 124-132.

Haghighi, S. R. M., Farahbakhsh, E., & Eskandari, M. (2015). Evaluation of antifungal activity of ZnO/Ag nanoparticles on Candida albicans biofilm.

Ying Wang, P. L. R. (2016). Biodegradable functional polycarbonate micells for Controlled release of amphotericin B. Acta Biomaterialia,

Desai, S. (2011). Development and evaluation of niosomal antifungal. IJPS, 2011.

Viswanad, L. T. (2012). Formulation and optimization of clotrimazole - loaded proniosomal gel. Scientia Pharmaceutica,

Teemu, J. N. P. K. (1998). Simvastatin but not pravastatin is very susceptible to

interaction with the CYP3A4 inhibitor itraconazole. *Clinical Pharmacology & Therapeutics, 63*(3), 332-341.

Liangti Qu, L. D. A. E. O. (2006). Shape/Size-Controlled Syntheses of Metal Nanoparticles for Site-Selective Modification of Carbon Nanotubes. JACS,