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A brief review of fluconazole as an antifungal agent and the need for research into its nanoformulation

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ABSTRACT

Purpose: Antifungals compounds have gained significant attention, and in this context, fluconazole as an antifungal is used predominantly, and the use of a nanoformulated form of this is discussed.

Design/methodology/approach: Fluconazole, an FDA-approved antibiotic, is an effective antimicrobial especially used to treat fungal infections. Its uniqueness lies in the fact that it contains fluoride with triazole functionality. Its efficacy against various types of fungus is demonstrated.

Findings: Although it is one of the effective antibiotics, its side effects are well documented, and due to this, many techniques are tried to improve its efficacy with lesser side effects.

Research limitations/implications: In this respect, nanoparticles play a crucial role, and many studies worldwide are carried out on this aspect. Among many nano techniques use of chitosan as well as lipid carriers of fluconazole are being considered. However, systematic studies are warranted to take this aspect into clinical trials.

Practical implications: Nano-based platforms seem to be an alternating hope to combat resistance and side effect.

Originality/value: A thorough study is the need of the hour to devise a proper nano-based strategy of fluconazole.

Keywords: Fluconazole, Antibiotic, Structure, Toxicity, Nanoformulation

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BIOMEDICAL AND DENTAL ENGINEERING AND MATERIALS

1. Introduction

The antimicrobial medication fluconazole (Fig. 1) (FNL) is suggested for exterior and systemic fungus infections. Its efficacy is attributable to the fluoride and triazole functionalities, which have resulted in the drug's improved solubility and use as a parenteral form. The FDA has approved FNL to treat candidiasis and other UTI infections.

FNL can also be used to treat coccidioidomycosis infections, and it can be used to treat pulmonary infections as well as soft tissue infections. In animal models, it is demonstrated to be effective against a) *Coccidioides immitis*, b) *Paracoccidioides brasiliensis*, c) *Histoplasma capsulatum*, d) *Cryptococcus neoformans*, e) *Candida spp.*, f) *Blastomyces dermatitidis*, g) *Aspergillus spp.*. For coccidioidomycosis increased dose is needed, and like itraconazole FNL is used effectively for treating blastomycosis and also cystitis due to its water solubility character [1].

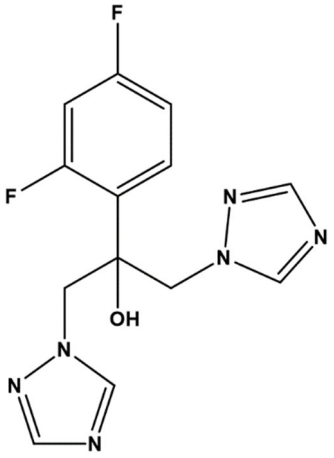

Fig. 1. Structure of fluconazole

When it comes to candidiasis, around 75% of women are impacted at some point in their lives, particularly during reproductive years, and it should be underlined that FNL has no known adverse effects or risks to the fetus [2]. It is alarming to note that when infected with *P. aeruginosa* the organism releases a toxic molecule that changes the antifungal effect of FNL.

Oral administration of FNL was found to be successful in the majority of patients with urinary tract candidiasis, and it was also found to be useful in the treatment of diabetes insipidus when vasopressin treatment failed. In cohort analysis, it was discovered that marrow candida infection was reduced in individuals receiving transplantation, while mould infection increased [3]. When patients were removed from catheter, administration of FNL orally was found to be safe but for a long time use, it was disappointing. While for AIDS pateints this remains the first choice of treatment for those affected with meningitis. For those patients who could not take itraconazole, FNL seemed to be the right choice, as this drug was able to cure around 70% of people with sporotrichosis [4]. For younger patients with leukemia, compared to caspofungin, FNL treatment reported lesser incidents [5]. FNL can be used in combination with other drugs for treatment or with dyes for photodynamic therapy.

2. Applications of fluconazole

For vaginitis, oral administration of FNL is also recommended [6]. Nail infection (onychomycosis) is generally treated with FNL and other azoles are also evaluated [7], and it is also used to treat biofilm of *C. albicans* via photodynamic therapy. The bioanalytical method (UHPLC-MS/MS) in an animal study with FNL led to enhanced exposure of ivosidenib in plasma while also inhibiting its metabolism [8]. Exploring the distribution of FNL in the skin as administered topically in topical administration via microdialysis as an invasive tool was used to find out skin pharmacokinetics of FNL. In vivo/in vitro action against candida was demonstrated more effectively for drug resistance organisms when FNL was combined with ribavirin. Even 0.2 per cent FNL was found to be penetrable for *C. keratitis*, suggesting that it could be used instead of amphotericin B [9]. In an i*n vitro* study, FK506 and four other azoles containing FNL exhibited promising results against *C. glabrata,* but further animal studies are required [10].

Repositioning drugs is considered for treating infections as they can increase pharmacological actions. Asdescribed by Zhongyi Ma et al [11] for treating deep fungal infection, and strategies to deliver antifungal agents, many methods to deliver drugs are summarised. In a review article, details on using FNL in treating eye infection safely indicated entry of FNL into ocular tissue [12]. Saikat Paul et al. demonstrated as a rapid screening technique – MALDI-TOF MS based AFST assay can be done to find resistance to fluconazole in *C. tropicalis* [13]. It was noted that the activity of azoles especially was found to be increased against *C. albicans* due to the metal binding activity as reported by Elizabeth W Hunsaker et al [14]. In a study, it was noted that combination of FNL along with methylene blue along with PDT resulted in effective elimination of *C. albicans* and *C. glabrata*. Genetic duplication resulted in enhanced FNL tolerance by fungal cells. Cecília Rocha da Silva et al. [15] demonstrated that amiodarone, with FNL, indicated good inhibition to *C. tropicalis* due to loss in integrity membrane and oxidative stress along with other changes leading to the death of fungus by apoptosis. Hunter et al. [16] demonstrated preceding FNL treatment on oral flora led to the alteration of flora.

3. Nanoformulation of fluconazole

Nanoparticles have various methods to combat germs; therefore resistance to free medications is considerably more common than resistance to pharmaceuticals following treatment with nanoparticles. The size/molecular weight of FNL is suitable for intravenous or oral administration but not for topical administration; hence nano form is chosen [17]. Nanotransfersome as a carrier and hyaluronic acid effectively delivered FNL for treating candidiasis in a study [18]. The use of solid lipid nanoparticles as a possible delivery system for FNL on resistant strains of candida is reported [19]. In yet another report, FNL loaded in rubber latex containing natural membrane indicated that this carrier can release FNL and prevent *C. albicans* growth, thus providing hope as a biomaterial for dermal applications. It is important to use the nano method to deliver drugs to lessen toxicity as it is noted that FNL can extend myocardial repolarization and QT interval need to be watched for patients treated with FNL alone [20]. FNL via the use of cubosome nanoparticles exhibited a promising treatment strategy for treating keratomycosis in rats [21].

Chitosan isolated from a fugal source (*Amylomyces rouxii*) was made as a nanoform to entrap FNL, and it was shown as an excellent strategy to control the growth of candida [22]. Many different nano cargo carriers have been shown to exhibit enhanced effects in inhibiting fungal pathogens, although an excellent strategy is yet to be derived [17]. Buccal nanoparticle (mucoadhesive) formulation with FNL was used to treat oral candidiasis. Madhu Gupta et al. [23] concluded from their study that nanostructured lipid carriers are a great candidate for dermal targeting effect with sustained/localized effect, for life-threatening fungal infection. Dnyanesh Takalkar et al. [24] paper focuses on understanding the mucoadhesive gel (vaginal) of FNL containing lipids of nano size as carriers to enhance deposition in tissues for combating vulvovaginal candidiasis. Mariana et al [25] aimed to design novel lipid nanocapsules with FNL for clinical therapy, with use in treating fungal infections *candida spp* that are resistant. Another study used an antisolvent precipitation approach to entrap FNL in Pluronic nanocarriers with the goal of enhancing ocular penetration. Entrapment will boost efficacy while maintaining compound safety and will be more effective at overriding azole resistance in Candida species. Antifungal activity of FNL was increased when tested against pathogenic fungi while silver nanoparticles were present, confirming a fold inhibition and the synthesis was environmentally friendly. Iron oxide nanoparticles, along with chitosan and FNL, showed effectivity in a better manner than FNL in inhibiting planktonic cells of Candida. Researchers linked FNL with copper/silver and zinc oxide nanocomposite and saw a 20-fold increase in activity, demonstrating the relevance of such techniques. This is especially true of antibiotics that are effective at reducing epidemic illnesses but have side effects when used at larger doses or for longer periods. Studies have looked at nano-FNL techniques for treating candida strains resistant to FNL alone as a first-line treatment.

4. Conclusions

Fluconazole is a promising medication for treating pathogenic fungal strains. However, despite the fact that fluconazole has numerous applications, its use is limited. Nano-based platforms appear to be a supplementary hope for combating resistance and negative effects. A thorough investigation is required to develop a fluconazole nano-based strategy.

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