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A Brief Review on Antifungal Containing Ketoconazole

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ABSTRACT
Fungal infections are the most common globally issue for skin health and it affected all age group but it common in adult. It infections are mostly treated by topical or systemic or specialanti-fungal therapy. Topical therapy is normally preferred because of their targeted therapy and less side effects.The some human diseases attributed in some way to the effects of fungi, and consequently have long been recognized as important to the dermatologist and mycologist. Thus, it is difficult to synthesize agents that will destroy the pathogenic organism and not harm to the patient. Ketoconazole is an imidazole derivative it was the first broad-spectrum, oral antifungal drug to be used in clinical medicine. This review summarizes recent advances in novel strategies employed in topical carriers to improve the therapeutic performance of anti-fungal Lotion.

Keywords – Ketoconazole, Antifungal lotion, Dermatophytosis, Pathogenic organism, Mycologist.

I. INTRODUCTION

Fungal infection is one of the major problems of skin disease across worldwide. Fungi normally attack the skin surface during the initial phase and later invade into the deeper layer by desquamation. Candida species is one of the fungi which are most superficial cutaneous infection [1-5]. Fungal infection expressed in deeper layer of skin called cutaneous mycoses". Cutaneous fungal infections are commonly known as "Dermatophytes". Fungi commonly involved in different dermatomycoses include Tinea corporis, Tinea pedis and Tinea cruris [6-8]. Once, fungal infection further penetrates deeper skin tissue is known as "Subcutaneous mycosis" [9].

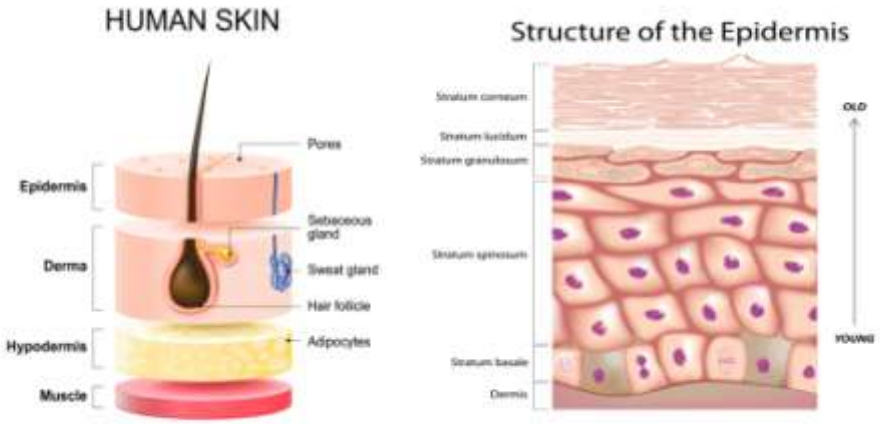

Fig – Skin

The Topical delivery of anti-fungal lotion is the best route against major skin dermatophytes. Topical delivery is contributes to reduced systemic toxicity and avoid pre-systemic metabolism. Various drugs like ketoconazole, are used as topical administration by spreading or smoothly rubbing on the skin [10-12]. The main advantages of topical delivery further include site specific drug delivery, reduce systemic toxicity, increase patient compliance, increase the efficacy of treatment and improve bioavailability. On the other hand, topical delivery of anti-fungal drugs can cause adverse skin reactions like allergic reaction and itching [13-16]. The anti-fungal activity of azoles is

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related to its ability to block the synthesis of ergosterol. Lipid formulation appears to be highly efficient carriers to improve fungicidal activity of azole drugs. Similarly, high skin penetration of topical antifungal formulations ought to be an important feature for effective treatment of cutaneous dermatophytosis. Particle size, surface charge, and lipophilicity play an important role in determining penetration depth into different skin layers.

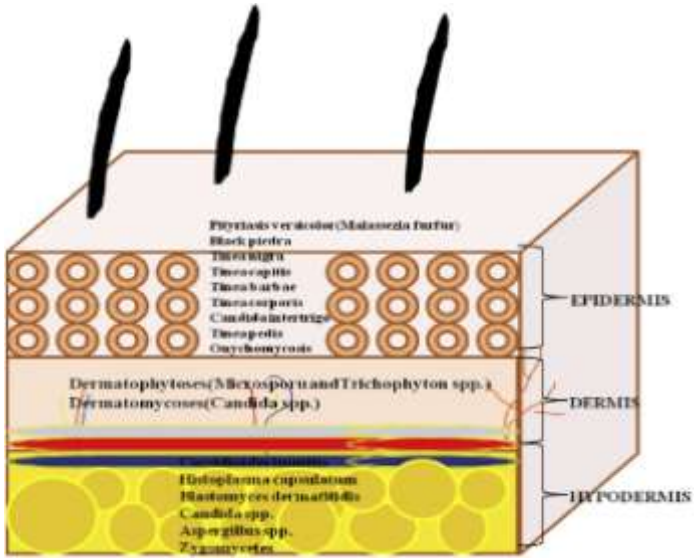

Fig – Layers of skin with Dermatophytoses

TYPES OF ANTIFUNGAL

The antifungal is divided into two types, local and systemic. Local antifungalare usually administered topically or vaginally, depending on the condition being treated. Systemic antifungalare administered orally or intravenously. of the clinically employed azole antifungals, only a handful are used systemically. These include ketoconazole, itraconazole, fluconazole, fosfluconazole, voriconazole, posaconazole, and isavuconazole. Examples of non-azole systemic antifungals include griseofulvin and terbinafine [17-20].

ORAL AND TOPICAL ANTIFUNGAL AND THEIR USE

Orally or topically routes of antifungal drugs or a combination of both can be used to treat fungal infections caused by dermatophytes [21]. All antifungal agents aimed at degrading the cell wall of the fungus to inhibit its mechanism of infection and to cause cell death. Topical antifungalare commonly thought of as a first-line treatment for dermatomycosis because as creams, liquids, or sprays they are treatments that can be directly applied to the skin, nails, hair, or even to the mouth and other places of body. Topical antifungalare more effective than systemic treatment, and their method of administration gives them the advantage of curing skin diseases by their direct application at the site of infection [22]. Candida infections, pityriasis versicolor, tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea faciei, tinea manuum, tinea nigra, and tinea pedis are examples of fungal infections that are treated with both first- and second-line topical antifungal drugs, depending on the severity of the infection [23,24].

The primary class includes azoles, polyenes, and benzylamine. On the other hand, in addition to drugs in the primary class such as ketoconazole, clotrimazole, econazole, , miconazole, and trioconazole, the drugs terbinafine and amorolfine are also used for the treatment of fungal infection. Ketoconazole shampoo is used to treat fungal infections on the scalp [25]. Antifungal injections are also available, such as amphotericin, flucytosine, itraconazole, voriconazole, anidulafungin, caspofungin, and micafungin, which are also used depending on the type of fungal infection. Antifungals are different from antibiotics because antibiotics can only kill bacteria [26].

Imidazoles and triazoles are the two types of azolesantifungal. Both work with the same

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mechanism, which is by stopping the conversion of lanosterol to ergosterol by inhibiting the work of enzyme lanosterol 14-alpha-demethylase, thus causing porousness in the fungal cell wall [27]. However, both categories show their activity at the different points of the spectrum and have structural differences in the number of nitrogen atoms: in imidazole, it is two, whereas triazole has three nitrogen atoms in it [28]. The polyene antifungals are nystatin, natamycin, and amphotericin B; they are effective against common fungal infections such as candidiasis, aspergillosis, mucormycosis, and cryptococcosis. Polyene antifungals bind to ergosterol, which is the main sterol present in the cell membrane, and they form a polyene–ergosterol complex that creates pores that increase cell permeability [29, 30]. On the other hand, amphotericin B shows fungicidal activity for Candida species, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces, and coccidioidesimmitis, although effective treatment depends on parameters such as drug amount and pH (6.0 to 7.5) [31]. Nystatin belongs to the polyene antifungal group and is effective against the mucosal and cutaneous infections caused by candida species, although it is less effective against dermatophytes [32]. Butenafine and allylamines are types of benzylamine drugs and are used topically for the treatment of dermatophytosis. They disturb the cycle of ergosterol synthesis by inhibiting squalene epoxidase enzyme synthesis. Allylamines are considered less effective antifungal agents; however, they have an advantage in the treatment of tinea pedis [33]. When the infection reaches a more severe level, second-line treatment with oral antifungal drugs such as griseofulvin, itraconazole, fluconazole, and terbinafine are among the medications mainly used, with allitraconazole being the most effective [34-39].

CANDIDA ALBICANS TREATMENTS BY BOTH ORAL AND TOPICAL ANTIFUNGAL TREATMENTS

Antifungal medications such as polyenes, azoles, and echinocandins are used to treat candidiasis in both topical and oral forms, depending on the severity of the infection. Nystatin and amphotericin B from polyene; miconazole, clotrimazole, itraconazole, ketoconazole, fluconazole, voriconazole, and econazole from azoles; and caspofungin, micafungin, and anidulafungin from echinocandins are used [40]. These are cyclic hexapeptides with an N-acyl aliphatic or aryl side chain that aid in the treatment of fungal infections caused by Candida and Aspergillus species by disrupting the fungus' cell wall structure [41]. Echinocandins named caspofungin, micafungin, and anidulafungin are mainly used and these are lipopeptides that act as an inhibitor of the β-d-glucan enzyme (the main component of cell walls) [42]. Therefore, the inhibition leads to cell death and helps to prevent the infection. The pathogenicity of candidiasis depends upon the host strength or factors by which yeast can multiply [43]. Upon candida infection, most microorganisms gather and form a three-dimensional structure on the surface, which is called biofilm [44]. These biofilms are resistant to amphotericin B and fluconazole antifungal drugs. However, the biofilm of Candida albicans is more pathogenic than all other species. For a long time, contaminations caused by Candida species were treated with azoles, the most common class of antifungal medications. As of late, protection from azoles has expanded in Candida species, both in clinical settings and in vitro. Azoles can treat infection by interfering with the catalyst lanosterol 14-α-demethylase [45]. This catalyst engages with the biosynthesis of a critical component, ergosterol [46]. Azoles mainly target components such as chitin and glucan, which are not present in human skin due to the structural difference between ergosterol and cholesterol [47]. Previously azoles and echinocandins were considered effective drugs against Candida species. However, nowadays, these species have become resistant to these drugs [48].

MECHANISM OF ACTION OF KETOCONAZOLE

Ketoconazole performas an antifungal agent by inhibiting the cytochrome P450 14α-demethylase enzyme. This enzyme is responsible for inhibiting the biosynthesis of triglycerides and phospholipids by fungi.More specifically, ketoconazole block the synthesis of lanosterol, a necessary precursor for ergosterol biosynthesis. Ergosterol is needed to maintain the integrity of the membrane of fungi.Without ergosterol, the fluidity of the membrane increase, which in turn prevents fungal growth, Ketoconazole, in high doses, can competitively bind to androgen receptors, such as that of testosterone and dihydrotestosterone, which can decrease the activity of testosterone and dihydrotestosterone in prostate cancer. Ketoconazole can also inhibit the enzymes 17-alpha-hydroxylase and 17, 20-lyase, which are

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necessary for the synthesis of steroids in the adrenal cortex, including testosterone.It inhibits the activity of the enzyme 21-hydroxylase, this enzyme is essential for synthesizing mineralocorticoids and glucocorticoids, such as cortisol, in the adrenal cortex.[49-53]

II. CONCLUSION

The many type of fungi are create form fungal infection, Antifungal medicines are used to treat fungal infections, which most commonly affect your skin, hair and nails. You can get some antifungal medicines from a pharmacy without needing a GP prescription. Antifungal medicines work by either: Killing the fungus preventing the fungus from growing. And there are so many uses of antifungal agents in the formation of medication, and antifungal have so many type for each antifungal disease give proper treatment. Ketoconazole is the mainstay antifungal agent for treatment of life-threatening mycoses and for most other mycoses, with the possible exception of the dermatophytes.

REFERENCE -

[1]. M. Ameen, Epidemiology of superficial fungal infections, Clin. Dermatol., 28 (2) (2010), pp. 197-201
[2]. B. Havlickova, M. Friedrich, Epidemiological trends in skin mycoses, Worldwide Mycoses, 51 (4) (2008), pp. 2-15
[3]. A.Y. Zhang, W.L. Camp, B.E. Elewski, Advances in topical and systemic anti-fungal, Clin. Dermatol., 25 (2) (2007), pp. 165-183
[4]. M. Ameen, Epidemiology of superficial fungal infections, Clin. Dermatol., 28 (No. 2) (2010), pp. 197-201
[5]. B. Havlickova, M. Friedrich, Epidemiological Trends in Skin Mycoses Worldwide, Mycoses, 51 (Suppl. 4) (2008), pp. 2-15
[6]. A.O. Goldstein, K.M. Smith, T.J. Ives, B. Goldstein, Mycotic infections. Effective management of conditions involving the skin, hair, and nails, Geriatrics, 55 (2000), pp. 40-45
[7]. T.J. Zuber, K. Baddam, Superficial fungal infection of the skin. Where and how it appears help determine therapy, Postgrad. Med., 109 (2001), pp. 117-123
[8]. B.B. Adams, Tinea corporis gladiatorum, J. Am. Acad. Dermatol., 47 (2002), pp. 286-290
[9]. F. Queiroz-Telles, M.R. McGinnis, I. Salkin, J.R. Gra ybill, Subcutaneous mycoses, Infect. Dis. Clin., 17 (2003), pp. 59-85
[10]. G. Sathyan, W.A. Ritschel, A.S. Husain, Transdermal delivery of tacrine. I. Identification of a suitable delivery vehicle, Int J Pharm, 114 (1) (1995), pp. 75-83
[11]. C. Magdum, N. Naikwade, R. Shah, Preparation and evaluation of fluconazole topical microemulsion, J. Pharm. Res., 3 (2009), pp. 557-561
[12]. M. Banerjee, A. Ghosh, S. Basak, Comparative evaluation of efficacy and safety of topical fluconazole and clotrimazole in the treatment of Tinea corporis, J. Pak. Assoc. Dermatol., 22 (4) (2012), pp. 342-349
[13]. S. Gungor, M. Erdal, B. Aksu, New formulation strategies in topical antifungal therapy, J. Chem. Dermatol. Sci. Appl., 3 (2013), pp. 56-65
[14]. H. Silva, G. Luz, C. Satake, Surfactant-based transdermal system for fluconazole skin delivery, J. Nanomed. Nanotechnol., 5 (5) (2014), pp. 1-10
[15]. A.Naik, Y.N. Kalia, and R.H. Guy, Transdermal drug delivery: overcoming the skin's barrier function, Pharmaceut. Sci. Technol. Today, 3 (2000), pp. 318-326
[16]. W.E. Dismukes, Introduction to antifungal drugs, Clin. Infect. Dis., 30 (2000), pp. 653-657
[17]. Dupont, B. (2002) Overview of the lipid formulations of amphotericin B. J. Antimicrob. Chemother. 49, 31–36
[18]. Zarif, L. Et al. (2000) Cochleates: new lipid-based drug delivery system. JJ. Liposome Res. 10, 523–538
[19]. Falk, R. Et al. (1999) A novel injectable water-soluble amphotericin B-arabinogalactan conjugate. Antimicrob. Agents Chemother. 43,1975–1981
[20]. Anonymous (2001) Liposomal nystatin – Nyotranw Antifungal. Drugs Future 26, 810
[21]. Sahni K., Singh S., Dogra S. Newer topical treatments in skin and nail

dermatophyte infections. Indian Dermatol. Online J. 2018; 9:149.

[22]. Hay R. Therapy of Skin, Hair and Nail Fungal Infections. J. Fungi. 2018; 4:99.

[23]. McKeny P.T., Nessel T.A., Zito P.M. Antifungal Antibiotics. StatPearls Publishing; Treasure Island, FL, USA: 2020.

[24]. Sahni T., Sharma S., Arora G., Verma D. Synthesis, Characterization and Antifungal Activity of a Substituted Coumarin and its Derivatives. Pestic. Res. J. 2020; 32:39–48.

[25]. Danielli L.J., Pippi B., Duarte J.A., Maciel A.J., Machado M.M., Oliveira L.F., Vainstein M.H., Teixeira M.L., Bordignon S.A., Fuentefria A.M. Antifungal mechanism of action of Schinuslentiscifolius Marchand essential oil and its synergistic effect in vitro with terbinafine and ciclopirox against dermatophytes. J. Pharm. Pharmacol. 2018; 70:1216–1227.

[26]. Pârvu M., Moţ C.A., Pârvu A.E., Mircea C., Stoeber L., Roşca-Casian O., Ţigu A.B. Allium sativum extract chemical composition, antioxidant activity and antifungal effect against Meyerozymaguilliermondii andRhodotorulamucilaginosa causing onychomycosis. Molecules. 2019; 21:3958.

[27]. Zhang A.Y., Camp W.L., Elewski B.E. Advances in topical and systemic antifungals. Clin. Dermatol. 2007; 25:165–183.

[28]. Jachak G.R., Ramesh R., Sant D.G., Jorwekar S.U., Jadhav M.R., Tupe S.G., Deshpande M.V., Reddy D.S. Silicon incorporated morpholine antifungals: Design, synthesis, and biological evaluation. ACS Med. Chem. Lett. 2015;6:1111–1116

[29]. Tutaj K., Szlazak R., Szalapata K., Starzyk J., Luchowski R., Grudzinski W., Osinska-Jaroszuk M., Jarosz-Wilkolazka A., Szuster-Ciesielska A., Gruszecki W.I. Amphotericin B-silver hybrid nanoparticles: Synthesis, properties and antifungal activity. Nanomed. Nanotechnol. Biol. 2016; 12:1095–1103.

[30]. Chowdhry S., Gupta S., D'souza P. Topical antifungals used for treatment of seborrheic dermatitis. J. Bacteriol. Mycol. Open Access. 2017; 4:1–7.

[31]. Nankervis H., Thomas K.S., Delamere F.M., Barbarot S., Rogers N.K., Williams H.C. Scoping systematic review of treatments for eczema. Program. Grants Appl. Res. 2016;4:1–480.

[32]. Shalini K., Kumar N., Drabu S., Sharma P.K. Advances in synthetic approach to and antifungal activity of triazoles. Beilstein J. Org. Chem. 2011; 7:668–677.

[33]. Ashbee H.R., Barnes R.A., Johnson E.M., Richardson M.D., Gorton R., Hope W.W. Therapeutic drug monitoring (TDM) of antifungal agents: Guidelines from the British Society for Medical Mycology. J. Antimicrob. Chemother. 2014; 69:1162–1176.

[34]. Prasad R., Shah A.H., Rawal M.K. Yeast Membrane Transport. Springer; Berlin/Heidelberg, Germany: 2016. Antifungals: Mechanism of action and drug resistance; pp. 327–349.

[35]. Dowd F.J., Johnson B., Mariotti A. Pharmacology and Therapeutics for Dentistry-E-Book. 7th ed. Elsevier Health Sciences; St. Louis, MO, USA: 2016.

[36]. Goldstein A.O., Goldstein B.G. Dermatophyte (Tinea) Infections. UpToDate; Walthman, MA, USA: 2017.

[37]. Waller D.G., Sampson T. Medical Pharmacology and Therapeutics E-Book. 5th ed. Elsevier Health Sciences; St. Louis, MO, USA: 2017.

[38]. Kaul S., Yadav S., Dogra S. Treatment of dermatophytosis in elderly, children, and pregnant women. Indian Dermatol. Online J. 2017; 8:310.

[39]. Rengasamy M., Chellam J., Ganapati S. Systemic therapy of dermatophytosis: Practical and systematic approach. Clin. Dermatol. Rev. 2017; 1:19.

[40]. Bondaryk M., Kurzątkowski W., Staniszewska M. Antifungal agents commonly used in the superficial and mucosal candidi-asis treatment: Mode of action and resistance development. Postepy Dermatol. Alergol. 2013; 30:293.

[41]. Mroczyńska M., Brillowska-Dąbrowska A. Review on Current Status of

Echinocandins Use. Antibiotics. 2020; 9:227.

[42]. Kofla G., Ruhnke M. Pharmacology and metabolism of anidulafungin, caspofungin and micafungin in the treatment of in-vasivecandidosis—Review of the literature. Eur. J. Med. Res. 2011; 16:159–166.

[43]. Marak M.B., Dhanashree B. Antifungal Susceptibility and Biofilm Production of Candida spp. Isolated from Clinical Samples. Int. J. Microbiol. 2018; 2018:1–5.

[44]. Harriott M.M., Lilly E.A., Rodriguez T.E., Fidel P.L., Jr., Noverr M.C. Candida albicans forms biofilms on the vaginal mucosa. Microbiology. 2010; 156:3635.

[45]. Spampinato C., Leonardi D. CandidaInfections, Causes, Targets, and Resistance Mechanisms: Traditional and Alternative Antifungal Agents. BioMed. Res. Int. 2013; 2013:1–13.

[46]. Chong P.P., Chin V.K., Wong W.F., Madhavan P., Yong V.C., Looi C.Y. Transcriptomic and genomic approaches for unrav-elling Candida albicans biofilm formation and drug resistance—An update. Genes. 2018; 9:540.

[47]. Long N., Xu X., Zeng Q., Sang H., Lu L. Erg4A and Erg4B Are Required for Conidiation and Azole Resistance via Regulation of Ergosterol Biosynthesis in Aspergillus fumigatus. Appl. Environ. Microbiol. 2016;83:e02924-16.

[48]. Pristov K.E., Ghannoum M.A. Resistance of Candida to azoles and echinocandins worldwide. Clin. Microbiol Infect. 2019; 25:792–798.

[49]. Van Tyle JH. Ketoconazole. Mechanism of action, spectrum of activity, pharmacokinetics, drug interactions, adverse reactions and therapeutic use. Pharmacotherapy. 1984 Nov-Dec; 4(6):343-73.

[50]. Hu Z, He B, Ma L, Sun Y, Niu Y, Zeng B. Recent Advances in Ergosterol Biosynthesis and Regulation Mechanisms in Saccharomyces cerevisiae. Indian J Microbiol. 2017 Sep; 57(3):270-277.

[51]. Bhasin S, Sikka S, Fielder T, Sod-Moriah U, Levine HB, Swerdloff RS, Rajfer J. Hormonal effects of ketoconazole in vivo in the male rat: mechanism of action. Endocrinology. 1986 Mar; 118(3):1229-32.

[52]. Engelhardt D, Weber MM, Miksch T, Abedinpour F, Jaspers C. The influence of ketoconazole on human adrenal steroidogenesis: incubation studies with tissue slices. Clin Endocrinol (Oxf). 1991 Aug; 35(2):163-8.

[53]. Loli P, Berselli ME, Tagliaferri M. Use of ketoconazole in the treatment of Cushing's syndrome. J Clin Endocrinol Metab. 1986 Dec; 63(6):1365-71.