Chapter

Cutaneous Candidiasis

Iqra Farzeen, Saima Muzammil, Azhar Rafique, Razia Noreen, Muhammad Waseem, Rahat Andleeb, Muhammad Umar Ijaz and Asma Ashraf

Abstract

Cutaneous candidiasis is a multipicture infection of the skin, generally caused by yeast like fungus *c.albicans* or other species of genus candida such as *candida parapsilosis, candida tropicalis, candida glabrata* but these species are unusual, secondary to skin diseases. *Candida* is flora of gut microbiota, rather than skin, although it is present on skin at some instances. Certain factor of candida species such as ability to evade host defense by biofilm formation, filamentous form and presence of tissue damaging enzyme phospholipase are attributed to pathogenicity. Cutaneous candida infection may occur in patient HIV/AIDS, cancer receiving chemotherapy, antibiotics, steroids therapy and in organ transplantation. Vesicles, pustules, maceration and fissuring are common symptoms on perineum, axilla and interriginous areas. Systemic and topical therapies are common treatment with different drugs. Single drug therapy as combination of anti-fungal, antibacterial and topical corticosteroid has marvelous results. Nystatin, Clotrimaziole and miconazole are efficiently reviewed topical drugs with 73–100% cure.

Keywords: *C.albicans*, pathogenicity, systemic therapies, topical therapies and drugs

1. Introduction

Fungi like to reside in different areas such as air, soil, waterbodies, nutriment, attire, human body, flora and fauna. Coccidioidomycetes, Histoplasmosis and blastomycosis are human mycoses, native to different geographical regions and may found in any organism [1]. However, few individuals, effected by inhalation of these dimorphic fungi, show symptoms. On the other hand, opportunistic fungal infection mostly caused by some fungal species such as Candida, Aspergillus and Zygomycetes species, it basically present in immunosuppressed patients [2]. Among opportunistic fungi Candida classified as particularly threatened species to diseased person with week defense system. Cutaneous candidiasis is a skin infection caused by *C. albicans*. From 20 species of candida, 30 are causing infection in human [3–5].

Medically most important species of genus candida are *C. albicans, C.krusei, C. parapsilosis, C. glbrata, C. guilermondii, C. tropicalis* and *C. kefyr*. Invasive candidiasis present in those who have immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS), hematological disorders and cancer and may involve any internal organ or site [6]. By ingesting and killing opsonized candida,

immune system is very useful in host body defense against invasive candida [7]. In immunodeificient patient such as innate anemia and impaired natural immunity by physiological abnormalities in phagocytic cells, candida is primary threat [8, 9]. Cutaneous candidiasis is well defined disease characterized by candida infection of skin [4]. So the present study was designed to review pathogenicity, causes, signaling pathways and drug delivery system having ability to accelerate accumulation of drug in different cutaneous layer.

2. Overview of common clinical feature of cutaneous candidiasis

A considerable ratio of healthy individuals carry detectable number colonizing candida on skin, oral, gastrointestinal tract. Oral candida account 25–75% in healthy population [10], colonize mostly on the surface of oral cavity and most frequently present in dorsum of tongue. Review of literature showed that oral candida was continuous and regular. Adherence on epithelium by *C. albicans* blastocconidia and hyphae followed integrin like molecule such as INT1p factor [11, 12]. Arginine-glycine-aspartic acid (RGD) sequence recognition by adhesion molecule on epithelial cells and themselves express RGD sequence identified by mammalian integrins enhance adhesion of yeast to epithelium. Carriages of Candida species rarely establish into mucocutaneous so cutaneous and mucosal candidiasis poorly progresses to invasive candida disease.

A well known cutaneous candidiasis fungal infection may categorized or may be limited to integument on limited body surface. Candida skin infection expresses by interdigital candidiasis between fingers and toe may develop after softening and torn away finger's skin. Like fungi, candida develops in hot, dark and humid area which answered why it occur between skin surface, close to each other. Fissuring, maceration, pimples and cyst are mostly present on interdiginious skin area. Candida also cause rashes affecting anus and buttock area usually known as diaper dermatitis. Rash is common causing agent of blanitis, spread to scrotum, thigh and gluteal area. Candida is major source of folliculitis in immunosuppressed and obese patients [13].

Approximately 1% outpatient [14] reported with common disease of skin, cutaneous candidiasis affect all life stages as compared to 7% [15] of all inpatient visits in skin medical centre. Candida is primary source of skin disease or may develop secondary to other skin infections such as allergic dermatitis, psoriasis or existing diaper dermatitis. Cutaneous candidiasis develop in all body regions but frequently manifestation include intertrigo, inflammation, diaper, rashes and candidiasis of finger web [14]. Diversification of albicans species present but *C. albicans* play major role in human skin candidiasis [14]. Synergetic *candida albicans* fungus origin of wide human pathologies ranging from persistent or mild mucocutaneous infection to acute, lethal and disseminated disorder. It colonize at mucosal surface or skin and progression into candidiasis in immunocompromising, barrier disruption or wide antibiotic use [16–18]. Fourth major reason of nosocomial infection is prevalence of cutaneous candidiasis by C. albicans, pledged with 20–80% fatality. CD4+ T cells play role in HIV+ /AIDS patients susceptible to oropharyngeal candidiasis paly role in defense of this candidiasis [19].

In finding related to human, Consequences of interleukins-23 and interleukins-17 pathway briefly evaluated to protect mice candidiasis. It is also showed that IL-23, IL-17RC and Act-1deficient mice are also vulnerable to oropharyngeal

candidiasis(OPC) [20–23]. Similar signaling pathway for cutaneous candidiasis is also described in mouse model [24–26]. Altogether, it is showed that mouse is faithful animal to study immune response in candidiasis.

The IL-17 cytokines family comprise 6 related members. Interleukins member-17A, 17B, 17C,17D,17E (Interleukins-25) and 17F [27]. Still, limited data available about antifungal function of IL-17 family cytokines aside from IL-17A and IL-17F. IL-17A and IL-17F signal by heterodimeric receptor composed of IL-17RA and IL-17RC [28, 29]. Additionally, IL17RA combine with other partner of interleukin-17 family of receptors to make a binding complex for other IL-17 family cytokines [30] and predicted as interleukin –17 family of receptors signaling subunit.

Specifically, receptor complex (Interleukins-17RA and interleukins-17RE has cytokines interleukins-17C signal [27]. In comparison to iterleukins-17F and 17A, a lymphocyte derived, interleukins-17C is mainly released by upper integumentary tissue layer and keratinocytes [27, 31]. IL-17C like IL-17A govern natural defense at mucosal surface and skin by invigorating chemokines, inflammatory cytokines and antimicrobial peptides production. Interleukins-17A and interleukin-17C translated genes overlapping [32–34]. It is reported that interleukins-17C magnify direct signaling response by T-helper17 on T-helper 17 cells by interleukins-17RE/17RA [35]. Many studies has demonstrated protective role of IL-17C in gut and skin, but it is still poorly understood [36–38].

Local skin condition like occlusion, incomplete skin barrier, humidity and altered microbial flora promote cutaneous candidiasis infection. Many risk factor are known such as medical or disease related immunosuppression, endocrine disorders, malnutrition, pregnancy, steroid therapy, malignant diseases and compromised blood flow [16, 39].

Human cutaneous candidiasis is noxious dermatotosis defined by visible and microscopic cyst that are basically polymorphonuclear leukocytes. Epicutaneous implementation of candida blastospore occlusion for 24 hours in rodents create intraepidermal microabscesses and subcorneal cyst at sites of hyphal invasion. Only two species *C. albicans and C. stellatoidea* produces lesion after penetration in skin, remaining species fail to elicit inflammatory response [40]. Chemotactic stimuli generation may be related to clinical mechanism accountable for neutrophil cellular migration. In vitro studied explained migration of polymorphonuclear leukocytes by *C. albicans.* This response dependent on heat labile serum factor and independent of organism's viability [41]. Stratum corneum act as barrier but only to few species of candida. After penetration barrier, complement system mediates an acute neutrophil pustular response by inhibiting candida proliferation and prevents deep invasion of tissue [40].

Candida, human mucosal microbiota, not of skin carries by fingers. By microscopy and culture cutaneous candidiasis characterized and clinical diagnosis established. In these days different techniques namely polymerase chain reaction (PCR) and matrix-assisted-laser-desorption–ionization time-of-flight-mass-spectrometry (MALDI TOF-MS) manifested sensitive, rapid, well characterized method of candidiasis identification [42, 43].

The differentiation between living and dead fungi require cultures. National treatment guidelines exist for few invasive yeast infection [44] but lacking for skin yeast infection. Current treatment includes wide range of oral and topical therapies with anti-fungal and anti-inflammatory effects. Furthermore, topical treatment with corticosteroid have been established, but it is not clear whether these are preferable or not.

3. Pathogenesis stages

3.1 Biofilm formation

C. parapsilosis, C. albicans and other species are capable of biofilm formation, promoting incursion and inhibit killing by antifungal therapy (**Figure 1**). Yeast, pseudohyphae, hyphae and germ tubes, are multiple morphologies of *C. albicans* are whereas those formed by *Parapsilosis* morphologies consist of only two cells type: hyphae and yeast. All these biofilm attaches to medical instruments and limited penetration of antifungals. Biofilm start by attachment of yeast cell with surface layer [45]. This explain the need to central line tube elimination to clear candidiasis and improve outcome [46].

3.2 Evading host immune system

C. albicans has mechanism to dodge normal immune response, making it vulnerable to premature infants who are immunocompromised. *C. albicans* can conceal its surface structure and improper *Candida* phagocytosis because its hyphae surface protein mimic receptor of complement system. Fungus gas ability to eradicate cellular C3b complement, minimizing immune response. In case, candida recognition, its

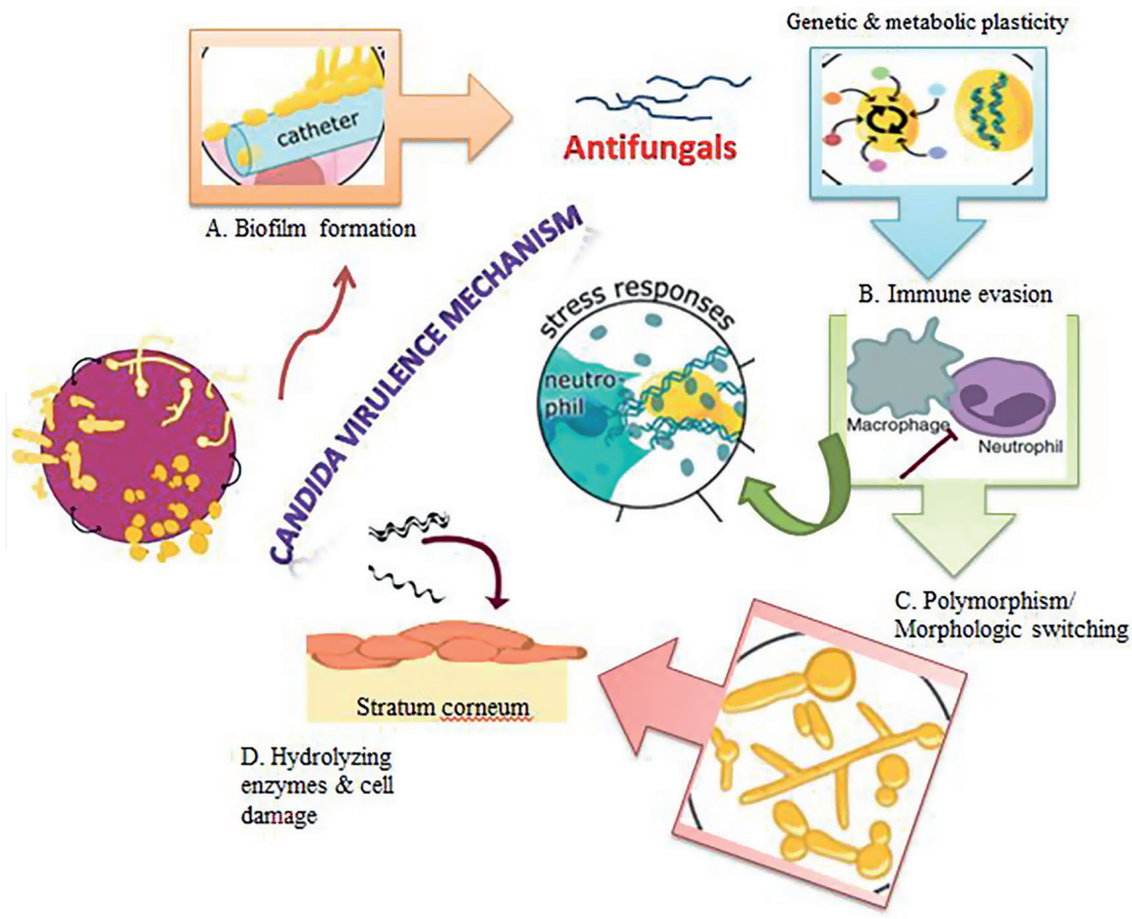

Figure 1.
Mechanism of C. albicans virulence. (A) Biofilm production, (B) evading host immune system, (C) morphologic switching, and (D) release of hydrolyzing enzymes.

hyphae involve in lysosomal fusion as well as elimination of macrophages to promote puncturing via filament elongation for destruction.

3.3 Morphologic switching

Morphologic switching shows capability of *C. albicans* to get both filamentous and yeast form. A filamentous hyphae exist in two forms either hyphae or pseudophyae. Changes in both form occur by ecological factor such as pH, temperature and amino acid presence. In vivo studies shows infection with wild type strain is more lethal and had greatest mortality rate than either filamentous only or yeast form [47]. The yeast form ease tissue and cell adhesion. In human cells, pseudohyphae enhance destruction and attenuated immune system. Another study indicated, both hyphal form of *C. albicans* are virulent, psudohyphal form has less virulency and can be more easily cleared from tissue as compared to hyphal form [48].

3.4 Hydrolyzing enzymes

C.albicans produced enzymes such as protease, phospholipase, lipase to accelerate digestion of epithelial cells and invasion in host tissue. A gene named as Int1 helped explain sticking mechanism, genes like *C. albicans* phospholipase B (caPLB 1) explain importance of phospholipase enzyme penetration in host cell [49]. Another group of enzymes, secreted aspartic acid (SAPs) help colonization of candida species. SAPs breaks different proteins including keratin and collagen, beneficial for host tissue [50]. Excluding *C. glabrtata,* almost all candida species produced SAPs*, C.albicans* produced highest amount of SAPs.

4. Virulence factors

There are many factors responsible for C. albicans virulence in colonization and intrusion of mucosal and cutaneous sites. The first indispensable step at epithelial cells, adhesion depend on upper surface elements of fungi affinity for epithelia. Candida adhesion molecule generally has three types.

One of these, a surface glycoprotein's protein constituent bind with arginine-glycine-aspartate (RGD), common to fibronectin, collagen, vitronectin and other extracellular matrix glycoprotein. In the second, binding of surface glycoprotein in lecithin like manner to sugar component of host glycoprotein. Surface mannoprotein a third one, least defined, polysaccharide constituent of candida attached with unknown host receptors. Different adhesion patterns have been reviewed in detail by calendar and Braun [51]. HIV/AIDS, mononucleosis, cancer and antibiotics can also increase risk of candidiasis [52]. Many studies suggested role of SAPs in colonization of oral epithelia [53]. Ex vivo analysis indicated, pepstatin inhibit a process, Pit formation by Candida albicans yeast in mouse corneocytes [54], which inhibit aspartyl proteinase enzymes, demonstrating Corneal layer invasion of proteinase. Pepstatin cannot hindered C. albicans attachment to corneocytes, only penetration, pointing out, colonization and adhesion of epidermal cells restricted by proteinase. Protein dependent penetration do not require morphologic alteration of yeast cell of candida to hyphae.

Hyphae formation is essential step for virulence and penetration of *C. albicans.* There is little evidence of hyphae role invasion, while yeast forms are associated with colonization. But hyphal form important colonizer in buccal epithelium So hyphae formation is not obligatory step for epidermal invasion. In vitro experiment shown hyphal property such as thigmotropism [55]. Histopathologic studies of *C.albicans* infected tissue, hyphae are unevenly distributed. Whereas keratinized cells have specific pattern along keratinocytes strata or perpendicular to it. Such pattern are not consistent as some plant fungal species exist perpendicular to cell boundaries.

It is suggested hyphae may prefer to grow appropriately towards all time available nutrients due to thigmotropism to micro surface in keratinized layer. A general factor, surface hydrophobicity, regulating cell adhesion by wander walls forces [56]. *C albicans* show wide hydrophobicity with respect to growth temperature [57], these variation associated with epithelial cell adhesion [58]. As a result hydrophobicity play role in pathogenesis of cutaneous candidiasis. Virulence factor by *C. albicans* rarely and discontinuously expressed in all possible microenvironment. There is no clear evidence to explain *C. albicans* high potential for rapid switching of expressed phenotypes [59] by transcriptional regulation expression [60]. This phenomena helpful to adapt different microenvironment to regulate gene expression of virulence during colonization and penetration [61].

5. Diagnosis

Adjunctive diagnosis is miracle, not any replaced culture but they useful only for high risk patients treated antifungal therapy and monitoring therapy response. Fungal outer membrane polysaccharide such as Beta-D-glucana de mannan and polymerase chain reaction assist detecting non-blood stream infection and treatment. Currently they do not give good result in identifying true infection and costly. BDG level is also helpful in detecting antifungal therapy. Serum BDG level in infants with invasion is 364 pg./ml vs.89 pg./ml in noninfected infants, decreases by antifungal therapy to 58 pg./ml [59].

Another assay to decide treatment therapy is direct buffy coated fluorescent assay [60]. In this analysis, fluorescent stain bind to cellulose and chitin containing structure. Fluorescent test helpful to recognize hyphae and spores following 2 hours duration. Bimolecular techniques such as PCR and DNA microarray technology, recognize fungi and its antifungal potential more quickly and with higher sensitivity than blood culture. PCR is helpful during higher fungal infection expression. PCR can detect candidiasis, nonblood stream infection, candida peritonitis and endotracheal colonization. Adjunctive test and PCR test are not critically studied.

6. Cutaneous candidiasis treatment

Immunocompromised patients are susceptible to fungal infection. The incidence of superficial and deep seated infection [62]. Cutaneous candidiasis is most common problem in human beings [63]. Various treatment strategies such as systemic therapy, topical drug treatment are used by different drug delivery system. Many treatment strategies are challenging and restricted to small group of compound, azole.

6.1 Systemic therapy

Systemic antifungal therapy is miracle for cutaneous candidiasis treatment with until complete remission occur with multiple week requirement. Various other infection such as catheter site and fungal digital escher are cured by continuous systemic therapy. Epithelization of skin lesion is helpful. Untreated primary skin infection extends far from visible range of lesion so systemic antifungal therapy applied before debridement (2–3 weeks). However, debridement role in neutropenic patient is unclear.

6.2 Treatment by fluconazole

A synthetic Trazole, fluconazole drug of 3rd generation is most preferable in clinical patients [64, 65]. FLZ is used as tablet and (i.v) injection, but restricted due to side effects such as skin and gastrointestinal irritation and taste disturbance. Application of solid lipid nanoparticles (SLN) and nanostructured lipid carrier (NLCs) for drug application in topical therapy of cutaneous candidiasis is another approach of encapsulation. The SLNS has great ability to direct active molecule and enhance therapeutic effectiveness with significant practicality of induction of lipophilic and hydrophilic drug. It has more efficacy, physical maintaince and low cost as compared to liposomes. Gold nanoparticles are also widely used in drug application [66].

Moreover, Physiological lipid core with epidermal attacking, follicular transfer and controlled emission of active molecule with increased skin hydration caused by occlusivity demonstrated high biocompatibility and biodegradability. Administration of FLZ require prolonged therapy, however systemic therapy application leads to disastrous by products [67]. It urges to develop fruitful FLZ preparation to avoid problem.

6.3 Treatment by Sertaconazole

Sertaconazole nitrate, a broad range topical antifungal factor belonging to azole class of drugs consisting of benzothiophene radical and excess lipophilic content [68, 69]. Synthesis reaction with lipophilic benzithiophene ether cause penetration of sertaconazole into keratinized layer of skin [70]. Similarly, these method recognize molecule without systemic absorption [70]. Chemical alteration to imidazole loop of sertaconazole nitrate boost up its in vitro antifungal activity against candida than other molecule of same antifungal class [68]. Sertaconazole nitrate shown high stability under different physiochemical condition [69].

6.4 Mechanisms of action of sertaconazole

Candida species show 3 main antifungal drug targets cell membrane, cell wall and nucleic acid [71]. It interacts with biosynthetic pathway of ergosterol by suppressing cytochrome P450-dependent 14 alpha-lanosteroldemethylase or Erg11p, regulated by ERG11 gene. This inhibition decreases addition of methyl to lanosterol to from ergosterol, hence ergosterol amount in fungal cell wall decreases resulting of toxic sterol mechanism intermediate humus to inhibit cell growth (**Figure 2**). Consequently, high lanosterol leads to absence of main fluidity, symmetry, permeability and integrity controlling factors [72–76]. Azole basically are fungistatic. Sertaconazole has an

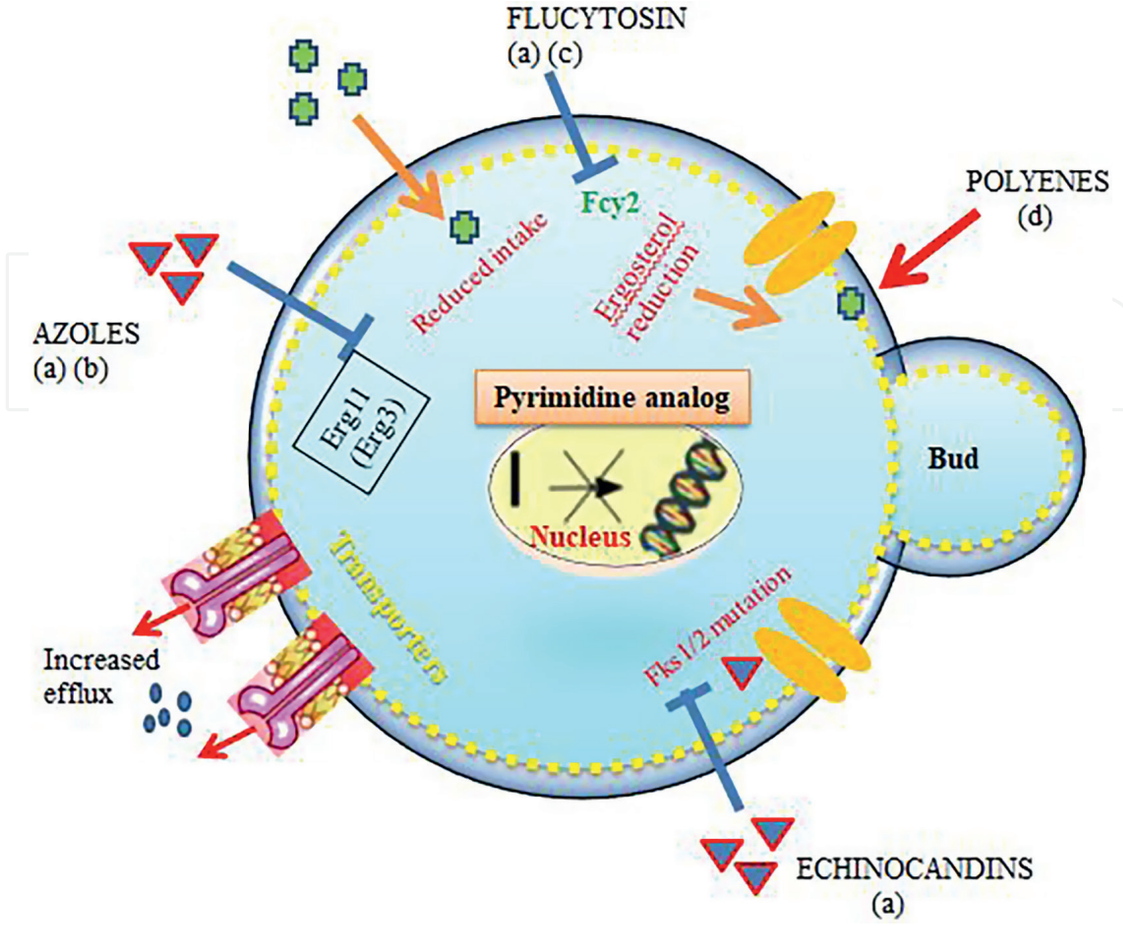

Figure 2.
Antifungal drug site of action in yeast-like cell.

additional effect, bind to nonsterol lipid of plasma membrane like other azoles, to change cell viability [77].

Azole and iron atom group of heme interaction leads to inactivation of 14 alpha-lanosterol demethylase blockage of yeast mycelium transformation. This step inhibit attachment of fungus to human skin surface, initial step of treatment [78]. Ketoconazole possess anti-fungal activity against Candida and dermatophyte infections, leading to KTZ development with hope that drug is not absorbed hence reduced drug related side effect. Although some studies have shown to moderate skin and eye irritation by using topical KTZ application, but systemic toxicity in anima is reported in literature [79]. Sertaconazole is also capable of inhibiting hyphae growth and conglomeration of shorter, poorly developed and cluttered blastocconidia [80]. Sertoconazole also bind directly with nonsterol lipid in the cell membrane in the absence of ergosterol synthesis, interacting permeability regulation, and cause leakage of intracellular components ATP, similar to miconazole and ketoconazole [81].

6.5 Topical therapy

It helpful for local treatment, noninvasive and applicable directly to site of action [82]. Topical formulation creams, lotion, gels, spray resulted in skin absorption, itching, thus failed to proper removal of yeast [83, 84]. In Switzerland, liposomal gel, 1st topical gel econazole established in 1994 [85, 86]. FLZ topical drug delivery

developed by gel micellar emulsion [87], gel designing [67], Organogel with lecithin content [88] and FLZ containing hydrogel [67] extensively studied.

For sustained drug release, skin aggregation for localized effect in skin and less permeation of drug required. So vesicular carrier is best and effective way of topical drug delivery [85, 86]. Vesicular carrier helped in best drug transfer, increase concentration and improved potency [89, 90]. Localization of drug at application site is characterized by vesicular carrier for reservoir, reducing dose, dosing frequency and systemic side effects [90].

6.6 Liposomal treatment

Over last few decades, fungal infection susceptibility and vulnerability upgraded in terms of frequency and major causative agent of death [91, 92]. Immunosuppressed patients are more prone than impaired immunity system [62]. Outer layer and deep seated infection rate rises gradually [93, 94] skin fungal infection is common problem, treatment strategy is challenging and limited to small number of compounds such as azole [63]. A wide range of azole antifungal agent are exploited, however, due to toxicity clinical use is restricted.

Phospholipid and nonionic surfactants containing liposomes and niosomes respectively more advantageous over conventional method. Niosomes and liposomes are analogous, best chemical structure, moderate cost and diversification of surfactant as compared to liposomal based vesicles. Most important characteristics are amphipathic nature allowing carring both hydrophilic and hydrophobic drugs [95, 96]. Liposome and niosomes act as dissolvable matrix and no specific point of drug delivery [97] Clotrimaziole loaded liposomes might be effective for skin candidiasis, as localized effect [83]. Literature reviewed that liposomes and niosomes have wide ability for TRA (Tretinoin) and niosomes carrying Ketoconazole are dominant over plain drug solution [98] showed that ketoconazole-containing niosomes offer a considerable advantage over plain drug solution. Literature reviewed that liposomes and niosomes have wide ability for Tretinoin and enhanced cutaneous drug accretion [96, 99–100]. Additionally, delivery of drug deeper layer of skin with highest accumulation of finasteride in follicular region is reported [97].

Similarly, toxicity of drug is lessened by drug pharmacology and bioavailability modification [101]. All these carrier system met desired sustained drug release characteristics versus local delivery. On the other hand, they show drawbacks such as liquid type and wash out problem. Furthermore, they can also be applied to commonly used dermal vehicle such as hydrogel, proper semisolid stability with appropriate dermal use [83, 102].

7. Conclusion

Genetic basis of immunodeficiency disease lead to best diagnosis and treatment and increased knowledge to pathophysiology of immune system. Clotrimaziole, nystatin and miconazole most important drugs with high clinical and mycological cure. Moving towards oral therapy, fluconazole only available evidence based option for systemic treatment. FLA loaded CA lipid based SLNs explained better activity against fungus by localized drug depot formation. This delivery system has great ability for dermal delivery of drug to treat cutaneous candidiasis. In perspective, resistance to candida species increases, these is need of further investigation and treatment option to reduce use of drugs.

Authors contributions

Iqra Farzeen, Rahat Andleeb, Asma Ashraf & Muhammad Waseem has substantially contributed to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work.

Saima Muzammil, Azhar Rafique & Razia Noreen participated in drafting or revising the work.

Rahat Andleeb, Asma Ashraf & Muhammad Umar Ijaz approved the final version of the work to be published.

Conflict of interest

The authors declare no conflict of interest.

Author details

Iqra Farzeen[1], Saima Muzammil[2], Azhar Rafique[1], Razia Noreen[3], Muhammad Waseem[4], Rahat Andleeb[1], Muhammad Umar Ijaz[5] and Asma Ashraf[1*]

1 Department of Zoology, Government College University Faisalabad, Pakistan

2 Department of Microbiology, Government College University Faisalabad, Pakistan

3 Department of Biochemistry, Government College University Faisalabad, Pakistan

4 Department of Environmental Science, Government College University Faisalabad, Pakistan

5 Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan

*Address all correspondence to: asmabinm@gmail.com

References

[1] Pfaller MA. Epidemiology and control of fungal infections. Clinical Infectious Diseases. 1994;**19**(Suppl. 1):8-13

[2] Koundal S, Cojandaraj L. Candida species–morphology, medical aspects and pathogenic spectrum. European Journal of Molecular & Clinical Medicine. 2020;**7**(07):4015-4021

[3] Pfaller MA, Diekema DJ. Epidemiology of invasive mycoses in North America. Critical Reviews in Microbiology. 2010;**36**:1-53

[4] Espinosa-Hernández VM, Morales-Pineda V, Martínez-Herrera E. Skin infections caused by emerging Candida species. Current Fungal Infection Reports. 2020;**14**:99-105

[5] Nurdin RSC et al. Cutaneous candidiasis caused by Candida kefyr. Pan African Medical Journal. 2021;**38**(178):1-8

[6] Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transplant Infectious Disease. 2010;**12**:220-229

[7] Maródi L, Johnston RB Jr. Host-fungal infections relevant to the newborn infant. In: Polin RA, Fox WW, Abman SH, editors. Fetal and Neonatal Physiology. 4th ed. Philadelphia, PA: Elsevier Saunders; 2011. pp. 1566-1569

[8] Rezaei N, Moin M, Pourpak Z, et al. The clinical, immunohematological, and molecular study of Iranian patients with severe congenital neutropenia. Journal of Clinical Immunology. 2007;**27**:525-533

[9] Segal BH, Herbrecht R, Stevens DA, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses study group and European Organization for Research and Treatment of Cancer consensus criteria. Clinical Infectious Diseases. 2008;**47**:674-683

[10] Cannon RD, Holmes AR, Mason AB, Monk BC. Oral Candida: clearance, colonization, or candidiasis? Journal of Dental Research. 1995;**74**:1152-1161

[11] Hostetter MK. RGD-mediated adhesion in fungal pathogens of humans, plants and insects. Current Opinion in Microbiology. 2000;**3**:344-348

[12] Hostetter MK. The iC3b receptor of Candida albicans and its roles in pathogenesis. Vaccine. 2008;**26**(Suppl. 8):108-112

[13] Maródi L. Mucocutaneous candidiasis. In: Stiehm's Immune deficiencies. Vol. 1. Tokyo: Academic Press; 2014. pp. 775-802

[14] Sei Y. 2011 epidemiological survey of dermatomycoses in Japan. Journal of Medical Mycology. 2015;**56**:129-135

[15] Peñate Y, Guillermo N, Melwani P, et al. Dermatologists in hospital wards: An 8 -year study of dermatology consultations. Dermatology. 2009;**219**:225-231

[16] Yost CC, Cody MJ, Harris ES, et al. Impaired neutrophil extracellular trap (NET) formation: A novel innate immune deficiency of human neonates. Blood. 2009;**113**:6419-6427

[17] Huppler AR, Bishu S, Gaffen SL. Mucocutaneous candidiasis: The IL-17 pathway and implications for targeted immunotherapy. Arthritis Research & Therapy. 2012;**14**(4):2

[18] Glocker E, Grimbacher B. Chronic mucocutaneous candidiasis and congenital susceptibility to Candida. Current Opinion in Allergy and Clinical Immunology. 2010;**10**:542-550

[19] Fidel PL. Candida-host interactions in HIV disease: Implications for oropharyngeal candidiasis. Advances in Dental Research. 2011;**23**(1):45-49

[20] Conti H, Peterson A, Huppler A, Brane L, Hernández-Santos N, Whibley N, et al. Oral-resident 'natural' Th17 cells and γδ-T cells control opportunistic Candida albicans infections. The Journal of Experimental Medicine. 2014;**211**(10):2075-2084

[21] Conti H, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann M, et al. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. The Journal of Experimental Medicine. 2009;**206**(2):299-311

[22] Ferreira MC, Whibley N, Mamo AJ, Siebenlist U, Chan YR, Gaffen SL. Interleukin-17-induced protein lipocalin 2 is dispensable for immunity to oral candidiasis. Infection and Immunity. 2014;**82**(3):1030-1035

[23] Ho A, Shen F, Conti H, Patel N, Childs E, Peterson A, et al. IL-17RC is required for immune signaling via an extended SEFIR domain in the cytoplasmic tail. Journal of Immunology. 2010;**185**:1063-1070

[24] van de Veerdonk FL, Kullberg BJ, Verschueren IC, Hendriks T, van der Meer JW, Joosten LA, et al. Differential effects of IL-17 pathway in disseminated candidiasis and zymosan-induced multiple organ failure. Shock. 2010;**34**(4):407-411

[25] Huang W, Na L, Fidel PL, Schwarzenberger P. Requirement of interleukin-17A for systemic antiCandida albicans host defense in mice. The Journal of Infectious Diseases. 2004;**190**(3):624-631

[26] Kagami S, Rizzo HL, Kurtz SE, Miller LS, Blauvelt A. IL-23 and IL-17A, but not IL-12 and IL-22, are required for optimal skin host defense against Candida albicans. Journal of Immunology. 2010;**185**(9):5453-5462

[27] Kashem SW, Kaplan DH. Skin immunity to Candida albicans. Trends in Immunology. 2016;**37**(7):440-450

[28] Toy D, Kugler D, Wolfson M, Van den Bos T, Gurgel J, Derry J, et al. Cutting edge: Interleukin-17 signals through a heteromeric receptor complex. Journal of Immunology. 2006;**177**(1):36-39

[29] Kuestner R, Taft D, Haran A, Brandt C, Brender T, Lum K, et al. Identification of the IL-17 receptor related molecule, IL-17RC, as the receptor for IL-17F. Journal of Immunology. 2007;**179**:5462-5467

[30] Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. Immunity. 2011;**34**:149-162

[31] Ramirez-Carrozzi V, Sambandam A, Luis E, Lin Z, Jeet S, Lesch J, et al. IL-17C regulates the innate immune function of epithelial cells in an autocrine manner. Nature Immunology. 2011;**12**(12):1159-1166

[32] Golden JB, McCormick TS, Ward NL. IL-17 in psoriasis: Implications for therapy and cardiovascular comorbidities. Cytokine. 2013;**62**(2):195-201

[33] Yamaguchi Y, Fujio K, Shoda H, Okamoto A, Tsuno NH, Takahashi K, et al. IL-17B and IL-17C are associated

with TNF-alpha production and contribute to the exacerbation of inflammatory arthritis. Journal of Immunology. 2007;**179**(10):7128-7136

[34] Li H, Chen J, Huang A, Stinson J, Heldens S, Foster J, et al. Cloning and characterization of IL-17B and IL-17C, two new members of the IL-17 cytokine family. Proceedings of the National Academy of Sciences of the United States of America. 2000;**97**(2):773-778

[35] Chang SH, Reynolds JM, Pappu BP, Chen G, Martinez GJ, Dong C. Interleukin-17C promotes Th17 cell responses and autoimmune disease via interleukin-17 receptor E. Immunity. 2011;**35**(4):611-621

[36] Friedrich M, Tillack C, Wollenberg A, Schauber J, Brand S. IL-36γ sustains a Proinflammatory Selfamplifying loop with IL-17C in anti-TNF-induced Psoriasiform skin lesions of patients with Crohn's disease. Inflammatory Bowel Diseases. 2014;**20**(11):1891-1901

[37] Martin DA, Towne JE, Kricorian G, Klekotka P, Gudjonsson JE, Krueger JG, et al. The emerging role of IL-17 in the pathogenesis of psoriasis: Preclinical and clinical findings. Journal of Investigative Dermatology. 2013;**133**(1):17-26

[38] Johnston A, Fritz Y, Dawes SM, Diaconu D, Al-Attar PM, Guzman AM, et al. Keratinocyte overexpression of IL-17C promotes psoriasiform skin inflammation. Journal of Immunology. 2013;**190**(5):2252-2262

[39] Del Rosso JQ, Kircik LH. Optimizing topical antifungal therapy for superficial cutaneous fungal infections: Focus on topical naftifine for cutaneous dermatophytosis. Journal of Drugs in Dermatology. 2013;**12**:165-171

[40] Ray TL, Wuepper KD. Experimental cutaneous candidiasis in rodents. The Journal of Investigative Dermatology. 1976;**66**:29-33

[41] Denning TJV, Davies RR. Candida albicans and the chemotaxis of polymorphonuclear neutrophils. Sabouraudia. 1973;**11**:210-221

[42] Maibach HI, Kligman AM. The biology of experimental human cutaneous moniliasis (Candida albicans). Archives of Dermatology. 1962;**85**:233-254

[43] Rebora A, Marples RR, Kligman AM. Experimental infection with Candida albicans. Archives of Dermatology. 1973;**108**:69-73

[44] Arendrup MC, Boekhout T, Akova M, Meis JF. ESCMID † and ECMM ‡ joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. Clinical Microbiology and Infection. 2014;**20**:76-98

[45] Talapko J, Juzbašić M, Matijević T, Pustijanac E, Bekić S, Kotris I, et al. Candida albicans. The virulence factors and clinical manifestations of infection. Journal of Fungi. 2021;**7**:79

[46] Benjamin DK, Stoll BJ, Fanaroff AA, et al. Neonatal candidiasis among extremely low birth weight infants: Risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics. 2006;**117**:84-92

[47] Bendel CM, Hess DJ, Garni RM, et al. Comparative virulence of Candida albicans yeast and filamentous forms in orally and intravenously inoculated mice. Critical Care Medicine. 2003;**31**:501-507

[48] Cleary IA, Reinhard SM, Lazzell AL, et al. Examination of the pathogenic potential of Candida albicans

filamentous cells in an animal model of haematogenously disseminated candidiasis. FEMS Yeast Research. 2016;**16**:11

[49] Leidich SD, Ibrahim AS, Fu Y, et al. Cloning and disruption of caPLB1, a phospholipase B gene involved in the pathogenicity of Candida albicans. The Journal of Biological Chemistry. 1998;**273**:26078-26086

[50] Naglik JR, Challacombe SJ, Hube B. Candida albicans secreted aspartyl proteinases in virulence and pathogenesis. Microbiology and Molecular Biology Reviews. 2003;**67**:400-428

[51] Calderone RA, Braun PC. Adherence and receptor rclationships of Candida albicans. Microbiological Reviews. 1991;**55**:1-20

[52] Udemezue O. Therapeutic Potential of Natural Compounds for Cutaneous VandidiasisTreatment using Murine Models. by Udemezue, O. I. May 2021. pp. 1-220

[53] Borg M, Ruchel R. Expression of extracellular acid proteinase by proteolytic Candida spp during experimental infection of the oral mucosa. Infection and Immunity. 1988;**56**:626-631

[54] Ray TL, Payne CD. Scanning electron microscopy of epidermal adherence and cavitation in murine candidiasis: A role of Candida acid proteinase. Infection and Immunity. 1988;**56**:1942-1949

[55] Sherwood J, Gow NAR, Oooday OW, Gregory OW, Marshall D. Contact sensing in Candida albicans: A possible aid to epithelial penetration. Journal of Medical and Veterinary Mycology. 1992;**30**:461-470

[56] Klotz SA, Drutz DJ, Zajic E. Factors governing adherence of Candida species to plastic surfaces. Infection and Immunity. 1985;**50**:97-101

[57] Antley PP, Hazen KC. Role of yeast cell growth temperatureon Calldida albicans virulence in mice. Infection and Immunity. 1988;**56**:2884-2890

[58] Hazen KC, Brawner DL, Riesselman MH, Jutila MA, Cutler JE. Differential adherence of hydrophobic and hydrophilic Candida albicans yeast cells to mouse tissues. Infection and Immunity. 1991;**59**:907-912

[59] Soli DR. High-frequency switching in Candida albicans. Clinical Microbiology Reviews. 1992;**5**:183-203

[60] Soli DR, Morrow B, Srikantha T. High-frequency phenotypic switching in Candida albicans. Trends in Genetics. 1993;**9**:61-65

[61] Soil DR, Galsask R, Schmid J, Hanna C, Mac K, Morrow B. Genetic dissimilarity of commensal strains of Candida spp carried in different anatomical locations of the same healthy women. Journal of Clinical Microbiology. 1991;**29**:1702-1710

[62] Soni N, Wagstaff A. Fungal infection: Focus on critical care: Antibiotics and ICU. Current Anaesthesia & Critical Care. 2005;**16**:231-241

[63] Calzavara-Pinton PG, Venturini M, Sala RA. Comprehensive overview of photodynamic therapy in the treatment of superficial fungal infections of the skin. Journal of Photochemistry and Photobiology B: Biology. 2005;**78**:1-6

[64] Ruhnke M, Hartwig K, Kofla G. New options for treatment of candidaemia in critically ill patients.

Clinical Microbiology and Infection. 2008;**14**:46-54

[65] Alekha KD, William FE. Fluconazole. In: Florey K, editor. Analytical Profiles of Drug Substances and Excipients. London, UK: Academic Press; 2006. pp. 57-113

[66] Kareem HA, Samaka HM, Abdulridha WM. Evaluation of the effect of the gold nanoparticles prepared by green chemistry on the treatment of cutaneous candidiasis. Current Medical Mycology. 2021;**7**(1):1-5

[67] Abdel-Mottaleb MMA, Mortada ND, El-Shamy AA, Awad GAS. Physically cross-linked polyvinyl alcohol for the topical delivery of fluconazole. Drug Development and Industrial Pharmacy. 2009;**35**:311-320

[68] Raga MM, Moreno-Manas M, Cuberes MR, et al. Synthesis and antimycotic activity of (benzo[b]thienyl) methyl ethers of 1-(2,4- dichlorophenyl)-2-(1H-imidazol1-yl)- ethanol and of (Z)-1 (2,4-dichlorophenyl)-2-(1H-imidazol-1-yl) ethanone oxime. Arzneimittel Forschung. 1992;**42**:691-694

[69] Albet C, Fernández JM, Sacristán A, Ortíz JA. Physicochemical properties, analytical determinations and stability of sertaconazole nitrate. Arzneimittel Forschung. 1992;**42**:695-698

[70] Farré M, Ugena B, Badenas JM, Márquez M, Roset P, Ortiz JA. Pharmacokinetics and tolerance of sertaconazole in man after repeated percutaneous administration. Arzneimittel-Forschung. 1992;**42**(5A):752-754

[71] Cannon RD, Lamping E, Holmes AR, et al. Candida albicans drug resistance—Another way to cope with stress. Microbiology. 2007;**153**:3211-3217

[72] Odds FC, Brown AJ, Gow NA. Antifungal agents: Mechanisms of action. Trends in Microbiology. 2003;**11**:272-279

[73] Ghannoum MA, Rice LB. Antifungal agents: Mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. Clinical Microbiology Reviews. 1999;**12**(4):501-517

[74] Akins RA. An update on antifungal targets and mechanisms of resistance in Candida albicans. Medical Mycology. 2005;**43**(4):285-318

[75] Hargrove TY, Friggeri L, Wawrzak Z, Qi A, Hoekstra WJ, Schotzinger RJ, et al. Structural analyses of Candida albicans sterol 14α-demethylase complexed with azole drugs address the molecular basis of azole-mediated inhibition of fungal sterol biosynthesis. Journal of Biological Chemistry. 2017;**292**(16):6728-6743

[76] Palacín C, Tarragó C, Ortiz JA. Sertaconazole: Pharmacology of a gynecological antifungal agent. International Journal of Gynaecology and Obstetrics. 2000;**71**(Suppl. 1): 37-46

[77] Carrillo-Muñoz AJ, Giusiano G, Ezkurra PA, Quindós G. Antifungal agents: Mode of action in yeast cells. Revista Española de Quimioterapia. 2006;**19**(2):130-139

[78] Agut J, Palacín C, Sacristán A, Ortiz JA. Inhibition of ergosterol synthesis by sertaconazole in Candida albicans. Arzneimittel-Forschung. 1992;**42**(5A):718-720

[79] Choi FD, Juhasz MLW, Natasha AM. Topical ketoconazole: A systematic review of current dermatological applications and future developments. Journal of Dermatological Treatment. 2019;**30**(8):760-771

[80] Figueras MJ, Cano JF, Guarro J. Ultrastructural alterations produced by sertaconazole on several opportunistic pathogenic fungi. Journal of Medical and Veterinary Mycology. 1995;**33**(6):395-401

[81] Agut J, Palacín C, Salgado J, Casas E, Sacristán A, Ortíz JA. Direct membrane damaging effect of sertaconazole on Candida albicans as a mechanism of its fungicidal activity. Arzneimittel Forschung. 1992;**42**:721-724

[82] Murdan S. Drug delivery to the nail following topical application. International Journal of Pharmaceutics. 2002;**236**:1-26

[83] Ning M, Guo Y, Pan H, Chen X, Zhongwei G. Preparation, in vitro and in vivo evaluation of liposomal/niosomal gel delivery systems for clotrimazole. Drug Development and Industrial Pharmacy. 2005;**31**:375-383

[84] Bidkar S, Jain D, Padsalg A, Patel K, Mokale V. Formulation development and evaluation offluconazole gel in various polymer bases. Asian Journal of Pharm. 2007;**1**:63-68

[85] Schreier H, Bouwstra J. Liposomes and niosomes as topical drug carriers: Dermal and transdermal drug delivery. Journal of Controlled Release. 1994;**30**:l-15

[86] Bouwstra JA, Honeywell-Nguyen PL, Gooris GS, Ponec M. Structure of the skin barrier and its modulation by vesicular formulations. Progress in Lipid Research. 2003;**42**:1-36

[87] Laithy HMEI, EI-Shaboury KMF. The development of cutina lipogels and gel microemulsion for topical administration of fluconazole. AAPS PharmSci. 2002;**3**:1-9

[88] Jadhav KR, Kadam VJ, Pisal SS. Formulation and evaluation of lecithin organogel for topical delivery of fluconazole. Current Drug Delivery. 2009;**6**:174-183

[89] Yimei J, Jolya L, Omria A. Liposomes as a carrier for gentamicin delivery: Development and evaluation of the physicochemical properties. International Journal of Pharmaceutics. 2008;**59**:254-263

[90] Manosroi A, Wongtrakul P, Manosroi J, Sakai H, Sugawara F, Yuasa M, et al. Characterization of vesicles prepared with various nonionic surfactants mixed with cholesterol. Colloids and Surfaces B: Biointerfaces. 2009;**30**:129-138

[91] Shao P, Huanga L, Hsueh P. Recent advances and challenges in the treatment of invasive fungal infections. International Journal of Antimicrobial Agents. 2007;**30**:487-495

[92] Ramsdale M. Programmed cell death in pathogenic fungi. Biochimica et Biophysica Acta. 2008;**1783**:1369-1380

[93] Donnelly R, McCarron P, Tunney M. Antifungal photodynamic therapy. Microbiological Research. 2008;**163**:1-12

[94] Segal E, Elad D. Fungal vaccines and immunotherapy. Journal of Medical Mycology;**16**:134-151

[95] Uchegbu IF, Vyas SP. Nonionic surfactant-based vesicles (niosomes) in drug delivery. International Journal of Pharmaceutics. 1998;**2006**(172):33-70

[96] Araujo VHS, Duarte JL, Carvalho GC, Silvestre ALP, Fonseca-Santos B, Marena GD, et al. Nanosystems against candidiasis: A review of studies performed over the last two decades. Critical Reviews in Microbiology. 2020;**46**(5):508-547

[97] Tabbakhian M, Tavakoli N, Jaafari MR, Daneshamouza S. Enhancement of follicular delivery of finasteride by liposomes and niosomes I. In vitro permeation and in vivo deposition studies using hamster flank and ear models. International Journal of Pharmaceutics. 2006;**323**:1-10

[98] Satturwar PM, Khandare JN, Nande VS. Niosomal delivery of ketoconazole. Indian Drugs. 2001;**38**:620-624

[99] Foong WC, Harsanyi BB, Mezei M. Biodisposition and histological evaluation of topically applied retinoic acid in liposomal, cream, and gel dosage forms. In: Hanin I, Pepeu G, editors. Phospholipids. 1990. pp. 139-154

[100] Sinico C, Manconi M, Peppi M, Lai F, Valenti D, Fadda AM. Liposomes as carriers for dermal delivery of tretinoin: in vitro evaluation of drug permeation and vesicle-skin interaction. Journal of Controlled Release. 2005;**103**:123-136

[101] Junginger HE, Hofland HEJ, Bouwstra JA. Liposomes and niosomes interactions with human skin. Cosmetics and Toiletries. 1991;**105**:45-50

[102] Pavelic Z, Skalko-Basnet N, Schubert R. Liposomal gels for vaginal drug delivery. International Journal of Pharmaceutics. 2001;**219**:139-149