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RESEARCH PAPER

MINI REVIEW ON DERMATOMYCOSIS

P.M. Ridzuan[1]*, C.M. Nazira[1], Manuel Ruth[1], C.N. Abdul Rassip[1], M.H Nur Raihan[2], Salwani Ismail[3], Nor Iza A. Rahman[3], E.A. Suzima[4], Hamdan Azhan[5]

[1]Department of Pre-Clinical, International Medical School, Management & Science University, 40100 Shah Alam, Selangor
[2]Department of Pathology, Hospital Selayang, 68100 Batu Caves, Selangor, Selangor
[3]Department of Basic Medical Sciences, Faculty of Medicine, Universiti Sultan Zainal Abidin, 20400 Kuala Terengganu, Terengganu, Malaysia
[4]Department of Family Medicine, Klinik Kesihatan Bukit Tunggal (KKBT), 21200 Kuala Terengganu, Terengganu, Malaysia.
[5] Department of Family Medicine, Klinik Kesihatan Manir (KKM), 21200 Kuala Terengganu, Terengganu, Malaysia.

*Corresponding author: pm_ridzuan@msu.edu.my

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Abstract

Dermatomycosis is a fungal infection of the skin, hair, and nail caused by *Trichophyton*, *Microsporum,* and *Epidermophyton*. These organisms are found in the environment, humans, and animals in forms of yeast or mold. There are many factors that contribute to the growth of fungal infections in human body. But still majority of virulent factors and mechanisms of the diseases of fungi are not clear. This review paper describes types of fungal infections, their classification, epidemiology and new insights into pathogenesis with the focus on molecular mechanisms of the diseases. Furthermore, traditional and novel molecular diagnostic methods and the variety of drug treatment and the development of resistance against these drugs are discussed.

Keywords: Dermatomycosis, classification, epidemiology, pathogenesis

INTRODUCTION

Fungi are one of the kingdoms in the living organisms and it can be classified into a few classes namely Zygomycetes (bread or pin molds), Basidiomycetes (mushrooms and toadstools), Ascomycetes (common mold) and Hyphomycetes (conidia mold). Classes separation was based on the method of spore production which is the sexual stage (teleomorph) and based on three subdivisions which are Zygomycota, Ascomycota, and Basidiomycota (Ellis, 2012). However, the fungi group classification process is not always easy because mycologist uses the fungi's characteristics and morphological structures to define the fungal species (Stchigel, 1999). Therefore, molecular and phylogenetic techniques is currently used for identification and classification of the fungi instead of morphological identification technique (Rodríguez-Tudela et al., 2008). Fungi can be categorized into two basic growth forms or stages which were yeast (unicellular form) and mold (filamentous fungi) (Mitchell, 1992). In yeast form, fungi can be easily identified through their morphology whereby yeast showed a single-celled fungus that produced simple budding to form

blastoconidia. Besides, yeast colonies were usually mucoid and moist in texture on the agar plate (Ellis et al., 2007). Examples of these fungi are *Candida* spp. and *Cryptococcus neoformans*. Meanwhile, filamentous fungi are vegetative fungi that produced filaments. The filament structure is packed tightly together and they produce spore called conidia (Ward & McCarthney, 2009). Many molds produce a special structure known as hyphae or conidiophores (Spicer, 2008). Thus, mold can be recognized by the morphology, spore production and arrangement of the hyphae (Dey, 1999).

Fungal pathogenicity

There were many major factors that influenced the fungal growth in the human body and emerged as a disease, which are temperature and immunological status of the host (Ellis, 2012). Besides nutrition and metabolism, infection routes, necrotic factor, and penetration are also the factors that influenced the fungi's ability to infect the human body (Burik & Magee, 2001). Fungi grow under optimum temperature of 37 °C and unable to grow at higher temperatures. Therefore, fungi have the ability to adapt in human body for survival (Mohd et al., 2010). Most fungi are saprophytic organisms in which they produce certain enzyme and the enzyme will react with host substrate to produce redox potential. Thus, fungi can survive in human body because their ability to adapt to host cellular defenses and tissue environments (Casadevall, 2007). However, the degree of fungi infection differs from one another since it depends on the amount of infection dose and tissue damage incurred by the fungi (Casadevall & Pirofski, 2000).

Type of fungi infection

Generally, there are three types of fungal infections namely superficial, systemic and opportunistic infections (Champoux & Neidhardt, 2004). Superficial fungal infections by yeast or mold affect the skin or mucosal membrane. This type of infection can lead to severe and systemic infection especially among immunocompromised individuals. In some cases, the infection spreads to other people. Most of the superficial fungal infections can be easily detected and efficiently treated (Kemna & Elewski, 1996). Examples of common superficial infections are candida vaginitis and athletes foot infection. Meanwhile, systemic fungal infection occurs when the fungi get into the bloodstream and cause more serious illnesses. In contrast to superficial fungal infection, systemic fungal infection can be life-threatening (Richardson, 2005). Opportunistic fungal infection occurs among people with low immune systems or patients who are on broad-spectrum antibiotics (Ward & McCarthney, 2009; Singh,2001). Frequently, opportunistic fungal infections are the main cause of morbidity and mortality among immunocompromised patients (Ascioglu & Rex, 2002).

Skin Mycology

Skin mycology is the study of fungi that are able to infect human skin and there are three groups of skin mycoses. Firstly, is a superficial mycosis which also known as superficial cosmetic fungal infections that infect the skin and hair (Ellis, 2013). In this infection, the fungi do not invade the tissue layer and no cellular reaction involved in the host. An example of common superficial mycosis includes pityriasis versicolor which is caused by *Malassezia furfur* (Mahmoudabadi et al., 2009). It is also known as tinea versicolor in reference to the variable pigmentation seen in the affected individuals. In rare condition, *M. furfur* can lead to fungemia once its invaded bloodstream especially via catheters (Aspiroz et al., 2002). Usually, superficial skin infection occurs among young adults. However, children and elderly people might also be affected due to lack of body immunity (Ellis, 2012). The second group of skin mycology is called cutaneous mycosis. This infection is caused by keratinophilic fungi because they have the ability to use keratin in the human body as a nutrient source due to the

presence of unique enzymes in the fungi which is called as keratinase enzyme (Rahul & Rajak, 2003).

Dermatophytes causing cutaneous mycosis can be categorized into three different broad epidemiological groups which are geophilic (normally inhibit the soil), zoophilic (mostly parasitized on animals) and anthropophilic (frequently parasitized on man and rarely infect animal) (Havlickova et al. 2008). Example of common fungi species that cause cutaneous mycoses is *Trichophyton* species such as *Trichophyton mentagrophytes, Trichophyton rubrum,* and *Trichophyton tonsurans*. Other species is *Microsporum* species, for example *Microsporum canis* and *Microsporum gypseum* (DiSalvo, 2014). The third category of skin mycosis is subcutaneous mycoses. This type of mycosis is a chronic infection of skin and subcutaneous tissue. They are localized infections. The agent for subcutaneous mycosis is all soil saprophytes fungi that have the capability to adapt to human tissue and cause disease in many ways (Ellis, 2012). There are three types of subcutaneous mycoses which are sporotrichosis, chromoblastomycosis, and mycetoma. Sporotrichosis is chronic mycosis of cutaneous or subcutaneous tissue that is caused by *Sporothrix schenckii* which may produce ulcerative and suppurative conditions (Greenwood et al., 2007). Fungi spread into muscle, bone and articular surface during secondary stage. The involvement of organs in systemic infection, for example the central nervous system, lung and genitourinary tract results in chronic infection (Engleberg et al., 2007). Chromoblastomycosis resulted from infection by pigmented fungi that produce crusted, verrucose and wart-like lesions to human body, which are also chronic in nature. Meanwhile, mycetoma characterized by draining sinuses, granules, and tumefaction is caused by many types of fungi and actinomycetes. Normally, the sinuses discharge granules of different sizes, colors, and levels of hardness (Ellis, 2012).

Dermatophytes

Dermatophytes belong to the group of filamentous fungi known as the ringworm fungi which are common skin diseases (Hayette & Sacheli, 2015). These fungi are composed of three closely related genera namely *Epidermophyton*, *Trichophyton* and *Microsporum* and are classified based on the formation and morphology of their conidia (structures of asexual reproduction) (Hayette & Sacheli, 2015; Peres et al., 2010). Dermatophytes are classified into zoophilic, geophilic or anthropophilic depending on their normal habitat (animals, soil and humans, respectively) (Peres et al., 2010). Among these groups, both zoophilic and anthropophilic dermatophytes are associated with skin infection while geophilic dermatophytes are rarely caused by human disease (Hayette & Sacheli, 2015). Skin is the first organ that exposed to the pathogenic organism. It is the most suitable human organ for fungi growth because skin represents a good ecological habitat for microorganisms to live on (Nester et al., 2007). One important dermatophyte species that significantly infects skin is *Trichophyton rubrum* which causes dermatophytosis (Bauman, 2007).

***Trichophyton* spp.**

Trichophyton spp. is a dermatophyte that lives in the soil, people or pets. The genus involves anthropophilic, zoophilic, and geophilic species related to its natural habitats. *Trichophyton spp.* is one of the most important triggers of human hair, skin, and nail infections. Most species of *Trichophyton* have teleomorphic shapes and the Arthroderma genus classifies these teleomorphs. There are several species in the genus *Trichophyton*. These includes *Trichophyton mentagrophytes, Trichophyton rubrum, Trichophyton schoenleinii, Trichophyton tonsurans, Trichophyton verrucosum,* and *Trichophyton violaceum*. The macroscopic characteristic demonstrates *Trichophyton* colonies slow to moderately fast development pace. The texture is waxy, cotton glabrous. The color appears to be white to bright yellowish beige or red-violet. The back is pale, yellow, brown or reddish-brown

(Doctor fungus, 2019) (Figure 1). The microscopic characteristics show septate, hyaline, conidiophores, microconidia, macroconidia, and arthroconidia. There were also chlamydospores found. Conidiophores are not well distinguished from the hyphae. Miroconidia is in the form of a single cell and round or pyriform. They are numerous and in groups they are isolated or organized. Microconidia is often *Trichophyton*'s predominant form of conidia. Macroconidia is cylindrical, clavate or cigar-shaped, multicellular, soft, small or thick-walled (Doctor fungus, 2019) (Figure 2).

Figure 1. Macroscopic feature of *Trichophyton spp.*

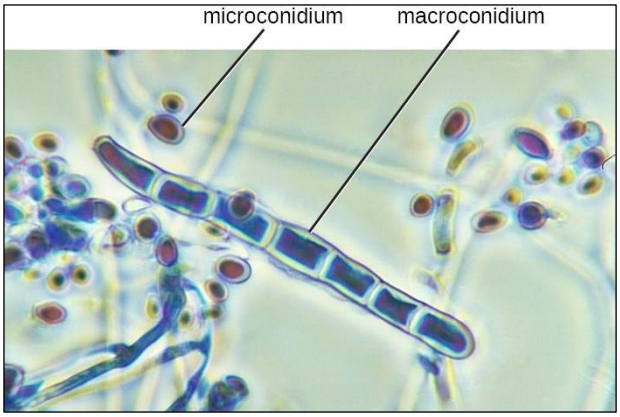

Figure 2. Microscopic feature showing hyphae (macroconidium) and microconidia of *Trichophyton rubrum* structure

Epidermophyton spp.

Epidermophyton spp. is a global distributed anthropophilic dermatophyte that often develops tinea pedis, tinea cruris, tinea corporis, and onychomycosis. Macroscopically, *Epidermophyton spp.* colonies tend to grow slowly without any particular culture growth. The colonies tend to create a dark yellow to greenish-brown or khaki-colored layer, elevated and folded in the middle, with a straight periphery and immersed growth fringe (Figure 3). The colonies' contrary color is from a burnt orange to sienna brown appearance. *Epidermophyton spp*. reveal septate and hyaline hyphae filamentous fungus microscopically (Figure 4). Hyphae is defined by soft, thin-walled, clavate, club-shaped macroconidia and the lack of microconidia, which distinguishes this species from other dermatophytes as well (David, 2019).

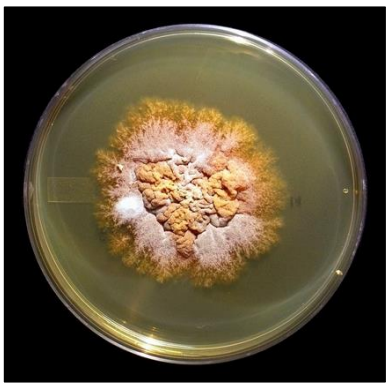

Figure 3. Macroscopic feature of *Epidermophyton floccosum*

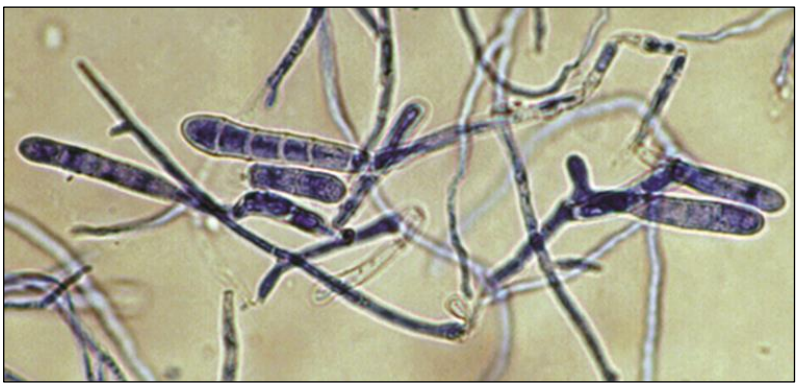

Figure 4. Microscopic feature of *Epidermophyton floccosum*

***Microsporum* spp.**

Microsporum spp. is a keratinophilic filamentous fungus included in the dermatophyte cluster. While some of the *Microsporum spp.* is a natural habitat. *Microsporum spp.* is the

asexual stage of the fungus and the Arthroderma genus is called the telemorphic phase. Macroscopic features indicate glabrous, downy, wooly or powdery colonies in *Microsporum* colonies. The growth of the colony can be slow or rapid on the colony's diameter ranges from 1 to 9 cm. The colony's color differs from species to species. It may be white to beige or yellow to cinnamon. It can be purple to red-brown from the back (Figure 5).

Figure 5. Macroscopic feature of *Microsporum audouinii*

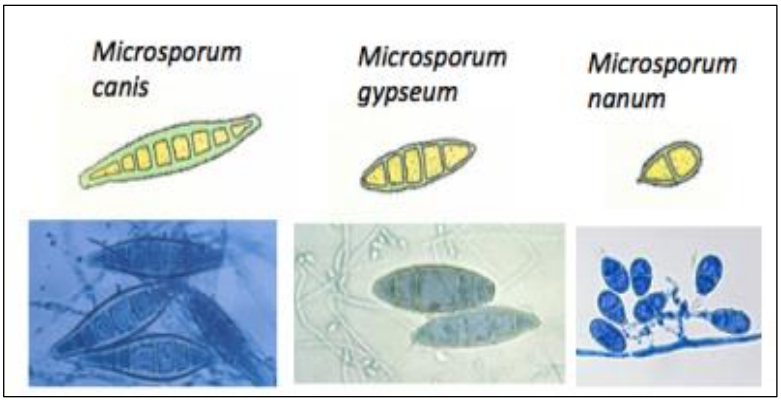

Figure 6. Microscopic feature of *Microsporum spp.*

When observed microscopically, *Microsporum spp*. produce hyphae septate, microaleurioconidia, and macroaleurioconidia. Conidiophores are similar to hyphae. Microaleuriconidia is soft, hyaline and thin-walled, unicellular, solitary, oval to clavate. Macroaleuriconidia is hyaline, roughened to echinulate, thin to thick-walled, typically fusiform and multicellular (2-15 cells). Often they have an annular frill (Figure 6).

Epidemiological aspects of dermatophytosis

Dermatophytosis is well established across the globe and its prevalence was estimated at about 20% ~ 25% of the world's population (Havlickova et al., 2008; Kim et al., 2016). Factors such as migration, tourism, immunocompromise of the host and changes in socioeconomic conditions have been linked with the epidemiology of dermatophyte infection (Kim et al., 2016). Besides, drug therapy conditions also associated in this context (Ameen, 2010). The causative species of dermatophyte infection vary across geographic regions. Species such as *Trichophyton rubrum*, *T. mentagrophytes var. interdigitale*, *Microsporum canis*, and *Epidermophyton floccosum* are distributed worldwide, while others have partial geographic restriction such as *T. schoenleinii* (Eurasia, Africa), *T. soudanense* (Africa), *T. violaceum* (Africa, Asia, and Europe), and *T. concentricum* (Pacific Islands, Far East, and India)(Ameen, 2010). In Western countries, epidemiological studies on dermatophytosis are reported everywhere (Drakensjö & Chryssanthou, 2011; Foster, 2004). A study conducted by Foster et al. at the Centre for Medical Mycology in Cleveland, Ohio found that *T. rubrum* was the most prevalent fungal pathogen in the United States as the incidence continues to escalate from 32% to 47% between 1999 and 2002 (Foster, 2004). In addition, the epidemiologic profile of dermatophytosis in Stockholm, Sweden revealed that *T. rubrum* was the predominant pathogen isolated from onychomychosis and tinea pedis cases (83.2%), while *Trichophyton mentagrophytes* only accounts for 7.4% (Drakensjö & Chryssanthou, 2011). In Asia, different studies have shown that the epidemiology of dermatophytosis varies across the region (Bassiri-Jahromi & Khaksari, 2009; Wu et al., 2011). Previous study conducted in a tertiary care hospital in South India found that *T. rubrum* was highly found in the study (58.9%), followed by *T. mentagrophytes* (24.6%) while *T. tonsurans* was predominantly found in those cases of tinea capitis (TC) (4/17 infections) (Hanumanthappa et al., 2012).

Another epidemiological survey of dermatophytosis conducted in Tehran, Iran, from 2000 to 2005 found that 92% of the dermatophytosis isolates were anthropophilic dermatophytes including *E. floccosum* (32%), *T. rubrum* (26%), *T. mentagrophytes* (19.9%), *T. tonsurans* (11.7%), *T. violaceum* (1.8%) and *T.schoenleinii* (0.7%) (Bassiri-Jahromi & Khaksari, 2009). Moreover, data from Ongoing National Survey for 1986, 1996 and 2006 on the trends of fungal infections in China found that the incidence of dermatophyte infections varies over time. In 1986, *T. rubrum* was much more prominent (47%) as compared to *T. mentagrophytes* (20%), while the incidence of *M. lanosum* and *E. floccosum* each of which accounted for 5% and 3%, respectively. As the observation continued in 1996, the highest incidence of pathogenic fungi was *T. rubrum* but the prevalence dropped slightly from 47% to 40% while *T. mentagrophytes* fell into third position (12%) after *Candida albicans* (23%). As for the year 2006, *C. albicans* appears to be the most common among all isolates (31%) followed by *T. rubrum* (30%), *T. mentagrophytes* (7%) and *C. glabrata* (7%) (Wu et al., 2011).

Pathogenesis of dermatophytosis

The mechanisms by which dermatophytes cause skin infection involves several steps; adhesion to the surface of the skin, invasion to the sub-layers by the penetration of fungal elements and secretion of enzymes that degrade the skin components (Kaufman et al., 2007). In order to cause disease, dermatophytes adhere to the surface of keratinized tissue to reach epidermis by germination of arthrocodium and then the hyphae enter the stratum corneum by penetration (Chinnapun, 2015). During penetration, a number of virulence enzymes and non-enzymes were produced for infection. These enzymes, such as protease, lipase, and cellulase which have different substrate specificities are essential for nutrient acquisition for growth and survival (Chinnapun, 2015). However, the key factor in the invasion and utilization of the stratum corneum of the host is protease enzymes (Liu et al, 2014). Protease enzymes are secreted in response to the presence of the skin components such as elastin in the dermis during tissue invasion (Kaufman et al., 2007; Chinnapun, 2015). Once in the host tissue, dermatophytes produce exo-enzyme keratinase and induce inflammatory reactions such as redness (ruber), swelling (induration) and heat and alopecia (loss of hair) at the site of infection (Lakshmipathy & Kannabiran,2010). Inflammation causes the pathogen to move away from the site of infection and take residence at a new site. This movement of the organism away from the infection site produces the classical ringed lesion.

Traditional and molecular diagnostic methods in fungal infection.

Early diagnosis for fungal infection is crucial to decide a viable treatment for the patient Therefore, vast and effective diagnostic method is required to achieve this goal. These diagnostic methods are in need to full fill the current demand of elevating fungi diversity that is associated with the establishment of immunosuppressive agents in mycoses as well as huge numbers of opportunistic pathogens especially in resource-limited countries such as South America, Southeast Asia and Africa (Marcos & Pincus, 2013). As been reported in literature survey, current diagnostic methods have some limitations such as time-consuming, less sensitivity and specificity which caused a delayed in giving treatments to patients (Marcos & Pincus, 2013). Determination of contagious fungal infection has dependent principally on strategies such as direct microscopic assessment, histopathology, and culture from clinical samples (Marcos & Pincus, 2013). These classical methods are not relevant nowadays as it required high levels of specific mycology training which could not be effectively done as the senior expert's loss in that field (Marcos & Pincus, 2013). However, despite the limitations, these classical methods still are used in laboratory especially culture. This method has advantages in yielding specific causative agents in fungal infection except for diagnosis of invasive fungal disease (IFD) which may take several days to determine treatment and to

worsen the case, this method may only become positive during the late infection (Marcos & Pincus, 2013).

Another classical diagnostic method is serological testing comprises the technologies such as immunodiffusion (ID), complement fixation (CF), tube precipitation test (IDTP), CF test (IDCF) and enzyme immunoassay (EIA). Among these methods, CF and ID are the most common serological tests been used for histoplasmosis (Marcos & Pincus, 2013). Histoplasmosis is fungal disease that infected lung of the patient (DeCherney & Berkowitz, 1982). CF detects IgG antibodies that were produced during convalescent phase or in choric infection. Whereas, ID favor in detection of IgM which has sensitivity >80% in diagnosis of acute primary coccidioidomycosis (Marcos & Pincus, 2013). All in all, EIA has broad spectrum in detecting IgM and IgG antibodies. Regardless, the serological results obtained from the diagnostic method may hardly to interpret due to inability to distinguish between current and previous infections.

In order to overcome the issues that have been raised, molecular diagnostics in clinical mycology became a help. Molecular diagnostic divided into two types; non-culture-based molecular diagnostic method and culture-based molecular diagnostic method. Non-culture-based molecular diagnostic does not require pure culture which can works without live cells if template nucleic acid is presence in the patient specimen. Polymerase chain reaction (PCR) has significant role in molecular identification methods which provides valuable data for selecting suitable therapies (Wollina, Nenoff, Haroske, & Haenssle, 2016). Diagnostic PCR comprises different approaches; conventional PCR and panfungal real time-PCR (Halliday, Kidd, Sorrell, & Chen, 2015). Ethidium bromide is used to stain the PCR products in conventional PCR whereas panfungal real-time PCR uses fluorescent dye during gel electrophoresis. The usage of fluorescent dye is to improve the specificity of nonspecific DNA-binding dye and specific labeled probe.

Culture-based diagnostic methods primarily use culture in all diagnostic assays and pure culture works the best in this field. With the enhancement from technologies, ribosomal sequencing became a major molecular approach in identifying fungal infection. Due to the nature of fungi and most eukaryotic microorganisms which have multicopy of ribosomal genes, ribosomal sequencing escalating the sensitivity during PCR amplification. This method is also known as PCR-based assay which targets only one or more regions in multicopy of rDNA gene cluster within large ribosomal subunit 18S, 5.5S, and 28S and intervening internal transcribed spacer (ITS regions) that comprise only two regions; ITS1 and ITS2 (Halliday et al., 2015). A proteomic approach such as MALDI-TOF MS (matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy) is one of the fastest non-nucleic acid sequence-based molecular diagnostic method for fungal identification. The advantages of using this newest approach are able to diagnose the sample in short time frame, no downstream data manipulation, and absence of prior suspicion of the isolated identity (Halliday et al., 2015).

Treatment for fungal infection

Treatment can be counted as sufficient when the patient shows an improvement from the previous signs and symptoms indicating the disease until an apparent cure including clinical cure (Sylvestre et al., 2018). A treatment approach may in the shape of topical or oral formulations. These treatment approaches are applied for dermatophytosis (infection of hair, skin, and nail) which normally topical treatment is for localized infections whereas extensive infections are more prone to oral treatments (Hay, 2018). Mycoses treatment are given based on the stages of infections as well as the patient's progression, comprises first-line treatment, alternatives and tertiary option (Gupta, MacLeod, Foley, Gupta, & Friedlander, 2017).

Between these treatments, different types of medication will be prescribed to the patient depending on the condition of patient.

Topical treatments have been reported having almost none serious harmful effects. Imidazole class of antifungal drugs has several drugs that are effective against tinea (ringworm) infection such as clotrimazole, econazole, miconazole, and ketoconazole (Hay, 2018). Interdigital tinea pedis can be treated with terbinafine cream which only takes about 7 days to fully recovered (Hay, 2018). In spite of the fact that terbinafine isn't yet authorized in all nations for use in youngsters, yet it is utilized as alternatives medicine for infections particularly brought by *Trichophyton* species and *Microsporum* species but in double standard dose (Hay, 2018). Other drugs such as butenafine, ciclopirox, clotrimazole, and efinaconazole are the first-line treatments of topical antifungals (Gupta et al., 2017). More seasoned cream or powder preparations such as tolnaftate or zinc undecenoate are available at drugs store which can be acquired without any prescription from specialists (Hay, 2018).

As mentioned earlier, oral treatments originally prescribed in cases of invasive infections of fungi due to its greater success and effectiveness (Hay, 2018; Gupta et al., 2017). In case of dermatophytes onychomycosis, terbinafine is the most commonly used antifungal medication to treat this disease which replacing the older treatment; itraconazole, griseofulvin and fluconazole (Hay, 2018). As been reported in the article, terbinafine recorded 35% of complete cure as compared to itraconazole treatment comprises 14% complete cure. However, itraconazole is effective against tinea cruris, tinea corporis, and dry type tinea pedis. This drug is very active against wide range of dermatophytes (Hay, 2018). However, many studies had been conducted due to limitations occurs in the current antifungal medications which have been reported showing elevated levels of nephrotoxicity and infusional poisonous quality. Azole and echinocandins also clinically reported having narrow spectrum of activity and development of fungal resistance against the available therapies (Chan, Cheah, Chong, Khor, & Teh, 2018).

CONCLUSION

Fungal infections of the skin and its appendages are among the most common diseases seen everyday practice. These infections usually causing local diseases may advance into systemic infections when host immune system weakened by variety of reasons. Fungi are currently classified using molecular and phylogenetic techniques instead of morphological identification techniques. They can be categorized into two basic growth forms or stages which were yeast (unicellular form) and mold (filamentous fungi). Most fungi are saprophytes. Opportunistic fungi survive in human body because they have the ability to overcome the host cellular defenses and able to adapt to the tissue environment. There are three types of fungal infections namely superficial, systemic and opportunistic infections. Skin mycoses are the most common diseases encountered in everyday life. These infections are usually localized in nature but they may spread and cause systemic infection especially in immunocompromised individuals. Common fungal infections causing cutaneous mycoses are caused by Dermatophytes (*Epidermophyton* species, *Trichophyton* species, and *Microsporum* species), which are filamentous fungi. The incidence of dermatophytosis varies for different places and the prevalence of the disease shows an increasing trend.

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