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Review on dermatomycosis: pathogenesis and treatment

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ABSTRACT

Dermatophytes, a group of keratinophilic fungi thriving on the keratin substrate are the etiological agents responsible for causing cutaneous infections. Dermatophytosis is currently treated with the commercially available topical and oral antifungal agents in spite of the existing side effects. Treatment of these cutaneous infections with secondary metabolites produced by marine microorganisms is considered as a novel approach. For many years these organisms have been explored with the view of developing antibacterial, antifungal, antiviral, anticancer and antiparasitic drugs. Exploring the unexplored aspect of actinobacteria for developing antidermatophytic drugs is a novel attempt which needs further investigation.

Keywords: *Trichophyton*; *Microsporum*; *Epidermophyton*; *Tinea Infections*; Novel Approach; Actinobacteria

1. INTRODUCTION

1.1. Dermatophytes

Infections pertaining to mankind particularly those affecting the keratinized tissues are of serious concerns worldwide and are increasing on a global scale. Dermatomycoses are infections of the skin, hair and nail caused as a result of colonization of the keratinized layers of the body. This colonization is brought about by the organisms belonging to the three genera namely *Trichophyton, Microsporum* and *Epidermophyton* [1,2]. Infection may also be caused rarely by the members of the genus *Candida* and by non-dermatophytic moulds belonging to the genera *Fusarium*, *Scopulariopsis* and *Aspergillus* [3,4]. Interestingly dermatophytic infections are predominant in the tropical and subtropical countries; especially in the developing countries like India where the hot climate and humid weather is favourable to the acquisition and maintenance of the disease [5,6] and currently no race is totally free from dermatophytoses.

2. ECOLOGICAL CLASSIFICATION

In the course of evolution these pathogens have developed host specificity. This host specificity is ascribed to the difference in the composition of keratin [7]. Based on their host specificity dermatophytes are classified into three ecological groups namely *geophiles* (soil), *anthropophiles* (man) and *zoophiles* (animals) [8]. The geophilic dermatophytes are generally saprophytic and derive nutrients from keratinous substrates. Rarely these pathogens cause infection in animals and man. Examples include *Trichophyton ajelloi*, *Trichophyton terrestre*, *Microsporum fulvum*, *Micropsorum gypseum*, *Microsporum cookie* and *Epidermophyton stockdaleae* [9-11].

Zoophiles are pathogens with only one animal host and grow as saprophytes on animal materials. Zoophiles are also reported to infect human beings. Human beings acquire the infection from infected animals. Examples include *Trichophyton simii* (monkeys), *Trichophyton mentagrophytes* (rodents), *Trichophyton equinum* (horses), *Microsporum canis* (cats) and *Micropsorum nannum* (pigs) [12,13].

The primary hosts of anthropophilic species are human beings but they may also cause infection in animals. Transmission of infection is from man to man. Examples include *Trichophyton rubrum*, *Trichophyton kanei*, *Trichophyton schoenleini*, *Trichophyton concentricum*, *Trichophyton tonsurans*, *Micropsorum gypseum*, *audouinii*, *Microsporum ferrugineum* and *Epidermophyton floccosum* [14,15].

2.1. *Trichophyton*

The genus *Trichophyton* includes 24 species. The colonies on agar media are powdery, velvety or waxy. The predominant spore type is micro conidia with sparse

macro conidia [16]. Reverse side pigmentation is characteristic of the species and is used for the identification of the species within the genus [17,18]. The macro conidia are thin walled with smooth surface and variable shape [19]. Some of the *Trichophyton* species are fastidious in their requirement for amino acid as nitrogen source. *Trichophyton tonsurans* requires ornithine, citrul-line and Arginine whereas *Trichophyton mentagrophytes* requires methionine. This nutritional specificity has been used by many authors in the identification of the *Trichophyton* species [19].

2.2. *Microsporum*

The genus *Microsporum* includes 16 species. The colony *morphology* of Microsporum species on agar surface is either velvety or powdery with white to brown pigmentation [16]. Both macro and micro conidia are produced but the predominant conidial structures are macro conidia. Micro conidia are less abundant. The macro conidia are multi septate with thick wall and rough surface [20]. Rarely some species produce neither micro nor macro conidia [21]. They do not have any special nutritional requirements.

2.3. *Epidermophyton*

The genus *Epidermophyton* includes only 2 species. The colonies are slow-growing, powdery and unique brownish yellow in colour. This genus is devoid of micro conidia. Macro conidia are abundant and produced in clusters [16]. These macro conidia are thin walled with smooth surface [20].

3. DISTRIBUTION FREQUENCY OF DERMATOPHYTES AND DERMATOPHYTOSIS

All the three genera of dermatophytes namely *Trichophyton*, *Microsporum* and *Epidermophyton* are worldwide in geographical distribution. The predominant cause of dermatophytic infections is *Trichophyton* followed by *Epidermophyton* and *Microsporum*. Within the genus *Trichophyton*, *Trichophyton rubrum* is the predominant etiological agent accounting for 69.5% followed by *Trichophyton mentagrophytes*, *Trichophyton verrucosum* and *Trichophyton tonsurans* [22-24].

According to the World Health Organization (WHO) survey on the incidence of dermatophytic infection, about 20% the people world wide present with cutaneous infections [25]. The disease does not spare people of any age [26]. Among the tinea infections the most predominant type of infection is *tinea corporis* or *tinea circinata* followed by *tinea cruris*, *tinea pedis* and *Onychomycosis*. *Tinea corporis* accounts for about 70% of the dermatophytic infection [26].

4. PATHOGENESIS AND CLINICAL PRESENTATION

The possible route of entry for the dermatophytes into the host body is injured skin, scars and burns. Infection is caused by arthrospores or conidia. Resting hairs lack the essential nutrient required for the growth of the organism. Hence these hairs are not invaded during the process of infection [27]. The pathogen invades the uppermost, non-living, keratinized layer of the skin namely the stratum corneum, produces exo-enzyme keratinase and induces inflammatory reaction at the site of infection [28-31]. The customary signs of inflammatory reactions such as redness (ruber), swelling (induration), heat and alopecia (loss of hair) are seen at the infection site. 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 [32] (**Figure 1**).

The infections caused by dermatophytes are commonly referred to as "*tinea*" or "ring-worm" infections due to the characteristic ringed lesions [33]. Based on the site of infection the tinea infections are referred to as *tinea capitis* (scalp), *tinea corporis* or *tinea circinata* (non-hairy, glaborous region of the body), *tinea pedis* ("Athletes' foot"; foot), *tinea ungium* ("*Onychomycosis*"; nail), *tinea mannum* (hands), *tinea barbae* ("Barbers' itch"; bearded region of face and neck), *tinea incognito* (steroid modified), *tinea imbricata* (modified form of

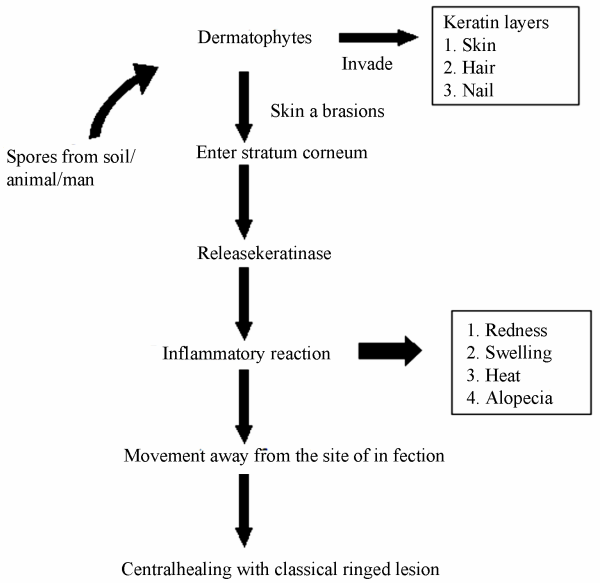

Figure 1. The schematic route of entry of dermatophytes into the host system and onset of immune response in the host in response to the pathogen entry.

tinea corporis), *tinea gladiatorium* (common among wrestlers') and *tinea cruris* ("Jocks' itch"; groin) [34].

5. IMMUNITY BEHIND DERMATOPHYTIC INFECTION

Host immune response to the invading pathogen is responsible for the clinical manifestations. The fungal pathogens induce both immediate hypersensitivity as well as cell mediated or delayed type hypersensitivity. Acquired resistance to the infection may also result from dermatophytic infection. The fungal growth is restricted by the inflammatory reactions produced as a result of infection with dermatophytes [35].

6. TREATMENT

Despite the advancements of science and technology, surprisingly the development of novel and efficient antifungal drugs is still lagging behind due to the very fact that fungi are also eukaryotic and have mechanisms similar to human beings [36]. Hence it becomes very difficult to develop an antifungal agent that is more specific in targeting the fungi alone without any damage to human beings. For successful treatment of the disease, proper diagnosis of the disease is always essential.

The treatment is chosen based on the infection site, etiological agent and penetration ability of the drug. The penetration ability and retention in the site of infection of the agent determines its efficacy and frequency of utility. Since the dermatophytes reside in the stratum corneum especially within the keratinocytes, the antifungal agents should have a good penetrating ability. The duration of treatment mainly depends on the type of infection and symptom. Generally a two-three week treatment is required for skin lesions whereas four-six week for feet inflammation [37].

Earlier, dermatomycosis was treated with the traditional topical antifungal agent *Whitfield's ointment*, a combination of 3% salicylic acid and 6% benzoic acid in a Vaseline base [38]. Next came into existence, *Castellani's paint*, a deep red coloured liquid, specifically effective against tinea ungium. Another topical preparation of importance was a combination of *silver nitrate* and *tincture iodine*. This preparation was effective against multiple lesions [39]. In general the dosage depends on the severity of infection, location and the efficacy of the drug. These topical preparations were applied twice a day for 2-3 weeks to prevent relapse condition. In addition to the above mentioned topical agents, tolnaftate, undecylenic acid, haloprogin, triacetin were in use for the treatment of dermatophytosis [39]. The year 1970 saw the release of Miconazole, the first in the line of azoles group. Since then many more were subsequently synthesized and added to this list during the same period. These antimycotic drugs belonged to the Azoles class of antifungal drugs. The major target of the azoles unlike the other antifungal agents is the cytochrome P_{450} enzyme [40] (**Figure 2**). Based on the number of nitrogen atoms the azoles derivatives are classified into 2 groups as imidazoles and triazoles [16].

Imidazoles include miconazole (1970), clotrimazole, ketaconazole (1978), econazole, bifonazole, tioconazole and oxiconazole [41]. The chronological order of the imidazoles to get FDA approval in United States is as follows miconazole (1974), econazole (1982), ketaconazole (1985), oxiconazole (1988) and clotrimazole (1993) [42]. The most recent drug to clear the FDA trials (2003) is Sertaconazole, a novel imidazole with broad spectrum antifungal activity [43]. In general the imidazoles exhibit side effects such as anorexia, constipation, headache, hepatitis, pruritis, exanthema and inhibition of synthesis of steroid hormone [44]. Triazoles include fluconazole, voriconazole, itraconazole (1980), posaconazole, teraconazole and ravuconazole. In comparison to the imidazoles, the triazoles exhibit lesser degree of side effects which includes nausea, dizziness and gastrointestinal upset [45]. Allylamines and benzyl amines were synthesized in the 1980s'. Allylamines include naftifine and terbinafine. Naftifine, terbinafine and benzylamine obtained FDA approval in United States in the year 1988, 1992 and 2001, respectively. The mode of action of these drugs is inhibition of the key enzyme squalene epoxidase, an essential enzyme involved in the synthesis of squalene epoxide from squalene [46] (**Figure 2**).

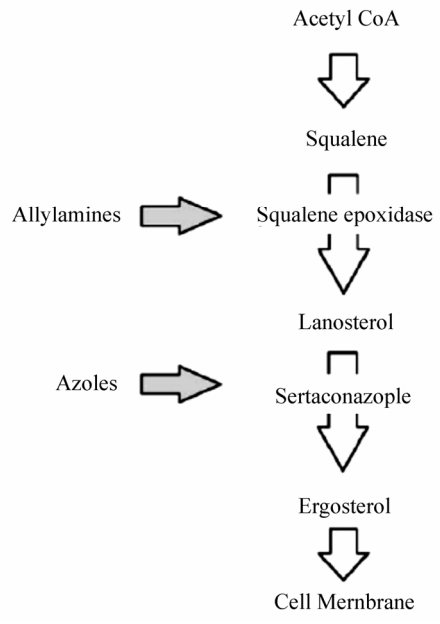

Figure 2. Schematic representation of the site of action of azoles, allylamines and benzyl amines.

Amorolfine, a morpholine drug targets the ergosterol synthesis similar to the azoles but at a site different from that of the azoles [47]. A new class of antifungal drug called hydroxypyridones became available since the year 2000. Ciclopiroxolamine, the representative drug of this class targets the cell membrane and affects the cell permeability. Apart from the above mentioned synthetic drugs many drugs such as Pyrrolo [1,2-a] [1,4] benzodiazepine with less side effects are being synthesized and experimented for treating dermatophytosis [48]. Griseofulvin, from *Penicillium chrysogenum* was isolated in 1930. Its antibacterial and antifungal potential was not fully understood until late 1950s'. It is the first antimycotic drug with a microbial origin [49]. Griseofulvin is a narrow spectrum antimycotic drug with fungistatic activity. It is very effective against all the dermatomycoses. The side effects include headache, nausea, bad taste, skin rash, systemic lupus erythematosus (SLE), porphyria and arthralgia. With all its side effects, griseofulvin still remains to be the gold-standard for treating dermatophytic infections [50]. Treatment of cutaneous infection using natural sources is the ongoing research work of many research groups across the globe. Compounds from the plants *Psorolea corylifolia* [51], *Azadirachta indica* [52], *Melaleuca alternifolia*, *Melaleuca dissitiflora*, *Melaleuca linariifolia* [53], *Nandina domestica* [54], *Didiscus oxeata* [55] have been reported to exhibit potential anti-dermatophytic activity. Further confirmation on the activity of these compounds is under investigation.

7. A NOVEL APPROACH TO SOLVE THE PROBLEM

More recently the scientific community has turned its attention to secondary metabolites from actinobacteria and its exploitation for various purposes which include therapeutic, environmental and industrial applications. With developing microbial resistance and need for safe and cost-effective antidermatophytic drugs, screening of actinobacteria for potential bioactive secondary metabolites becomes indispensible [56]. About 75-80% of the antibiotics that are available in the market are derived from *Streptomyces* [57]. To the best of our knowledge antidermatophytic secondary metabolite from *Streptomyces rochei* AK39 is the first report on antidermatophytic activity of actinobacteria [58]. Our investigation on the antidermatophytic activity of *Streptomyces* spp isolated from the saltpan region yielded three potential strains. The morphological, physiological and biochemical properties of these three potential isolates namely VITDDK1, VITDDK2 and VITDDK3 have been studied and reported [56,57]. The 16 S rRNA sequence of three strains *Streptomyces* spp. VITDDK1, *Streptomyces* spp. VITDDK2 and *Streptomyces* spp. VITDDK3 was submitted to the GenBank, NCBI under the accession numbers, GU223091, GU223092 and GU223093 respectively. The antidermatophytic activity of these three strains is anticipated to be due to high salt concentration of the environment. Under stress conditions microorganisms inhabiting the particular environment is said to produce complex chemicals that can be exploited medicinally.

8. CONCLUSIONS

The management of dermatophytic infections needs personal hygiene, awareness of infection, proper diagnosis and medication. At present there are a large number of antidermatophytic drugs available commercially. With increasing incidence of fungal infection, microbial resistance to the existing drugs, cost and side effects, there is a need for an antifungal drug that can overcome all these limitations. *Streptomyces* remains to be an unexhausted source of bioactive compounds and a boon to the medical field. Screening of Streptomyces from stressed environment can be a novel approach for obtaining potential lead molecules for clinical trials and later treatment of dermatomycosis.

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