Major challenges in dermatophytosis treatment: current options and future visions

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There is no part of the world can be cleared of the infection with dermatophytosis. Millions of persons and animals around the world are infected with specialized filamentous fungi called superficial infections of which dermatophyte are the most common agents. Dermatophyte infection incorporates a broad range of diseases involving particularly the nails, hair, and the skin. These infections were considered the most common causative agents of a patient visiting the dermatology. Dermatophytosis is mainly due to different species of dermatophytes that infect the cutaneous layer of the skin. There are many problems in the treatment of dermatophytosis that deserve to highlight because few studies have discussed this issue, especially dermatophyte management challenges became the state of anxiety in physicians and causing alarming distress to the patients recently. So the current review may serve as an impetus for researchers working in the field of medical mycology and antifungal drug design, as well as rationally reports and critically analyses the available knowledge by focusing and mentioning future steps strategies trying to find appropriate solutions regarding challenges in dermatophytosis management.

Keywords:
antifungal drug, antifungal resistance, dermatophyte, dermatophytosis

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Introduction

Superficial mycoses are among the most frequent forms of human infections, affecting more than 20–25% of the world's population [1,2]. Dermatophytosis is caused by dermatophytes [3]. It is considered a prevalent skin disease worldwide [4]. These diseases should be differentiated from other cutaneous fungal disease [5,6]. Dermatophytes are a special group of keratinophilic fungi which can live on keratin-rich materials that are found in soil or the human and animal skin [7–9].

The resistance of dermatophyte species to antifungal drugs was elevated significantly because of the increase in the number of persons with a deficiency in the immune system [10,11], Immunocompromised patients with prolonged prophylaxis antifungal agents leads to the emergence of resistant strains of dermatophytes. Unfortunately, the widespread use of antifungal agents to treat these infections has led to the development of drug resistance. Thus, drug resistance in pathogenic fungi, including the dermatophyte, is of increasing importance [11].

Dermatophytosis can occur in human and animals [12–14]. In-vitro test of any new drug is always considered the first step to evaluate its therapeutic activity, followed by choosing a suitable animal model *in vivo* to determine the therapeutical nature of such a new drug [15,16]. Dermatophytosis to be cured usually requires at least 2 weeks to a month in all dermatophyte infection approximately; however, it requires about 6 months in cases of tinea onychomycosis [17].

Chronic dermatophyte infections have been observed in the last few years with increasing prevalence and incidence among various regions [18]. Traveling and migration have a crucial role in the prevalence of dermatophytosis. The contagious nature of dermatophytosis make it easy to spread from person to another or from animals to humans.

As with any antimicrobial drug, antifungal agents have adverse effects. Dermatophytosis management became a true problem in some people like the elderly, pregnant women, and children because some antifungal drugs may have dangerous side effects [19]. The vaccine for dermatophyte infection is unavailable for humans at this moment.

This review focuses on understanding the major problems in the treatment of dermatophyte infection

by providing a rational and critical discussion on the available knowledge to obtain a clear future vision regarding dermatophytosis management.

Antifungal resistance in dermatophytes

In general, clinical antifungal resistance is defined as persistence of infection or symptoms in spite of administration of appropriate antifungal agents, and consequent failure to eliminate the fungal infection.

Drug resistance in dermatophyte infection is so important an issue [10]. Antifungal drug resistance of dermatophyte and other pathogenic mycoses increased alarmingly, due to elevated numbers of persons with HIV [10,11], long living of these patients with antifungal agent treatment lead to the emergence of resistant strains of pathogenic microbes including dermatophytes [11]. Dermatophyte drug resistance emerged in seven isolates from 36 dermatophytes revealed resistance to one or more drugs such as itraconazole, ketoconazole, and voriconazole in addition to fluconazole [20].

The prevalence of azole resistance in dermatophytes has been reported to be as high as 19% in certain areas worldwide [11]. Consequently, the evaluation of antifungal susceptibility of dermatophytes is important for the surveillance of antifungal resistance development.

To evaluate dermatophyte resistance pattern test, 80 patients of all age groups with a clinical diagnosis of dermatophytosis were involved. Resistance against fluconazole and terbinafine was the most common, representing 61.33 and 48%, respectively. Resistance against fluconazole was noted among all species of dermatophytes, followed by terbinafine and clotrimazole. Therefore, the increasing trend of resistance against dermatophyte treatment should be based on antifungal sensitivity testing [21].

The major drug resistance mechanisms in dermatophytes are efflux pump proteins overexpression and biofilm formation [22,23], modifications of target enzymes, overexpression of genes encoding ATP-binding cassette transporters and stress-response-related proteins [10] (Fig. 1).

There are uncompleted information regarding the mechanism of antifungal agent resistance regarding the crucial problem in dermatophyte infection treatment, so more studies are demanded to increase our information about the nature of resistance mechanisms in dermatophytes.

It is necessary to search for new drugs because of the increase of resistant isolates [24]. Terbinafine resistance has been recorded for the first time clearly in 2003 [25]. Furthermore, six isolated *Trichophyton rubrum* resistant to terbinafine have also been reported [26]. Another study revealed resistance of *T. rubrum* to terbinafine with a minimum inhibitory concentration of more than 4 μg/ml [27]. Antifungal agent resistance may be enhanced and increased by recurrent dermatophyte infections that lead to the emergence of new strains that have the ability to resist conventional antifungal drugs [11].

Limited number of antifungal agent availability

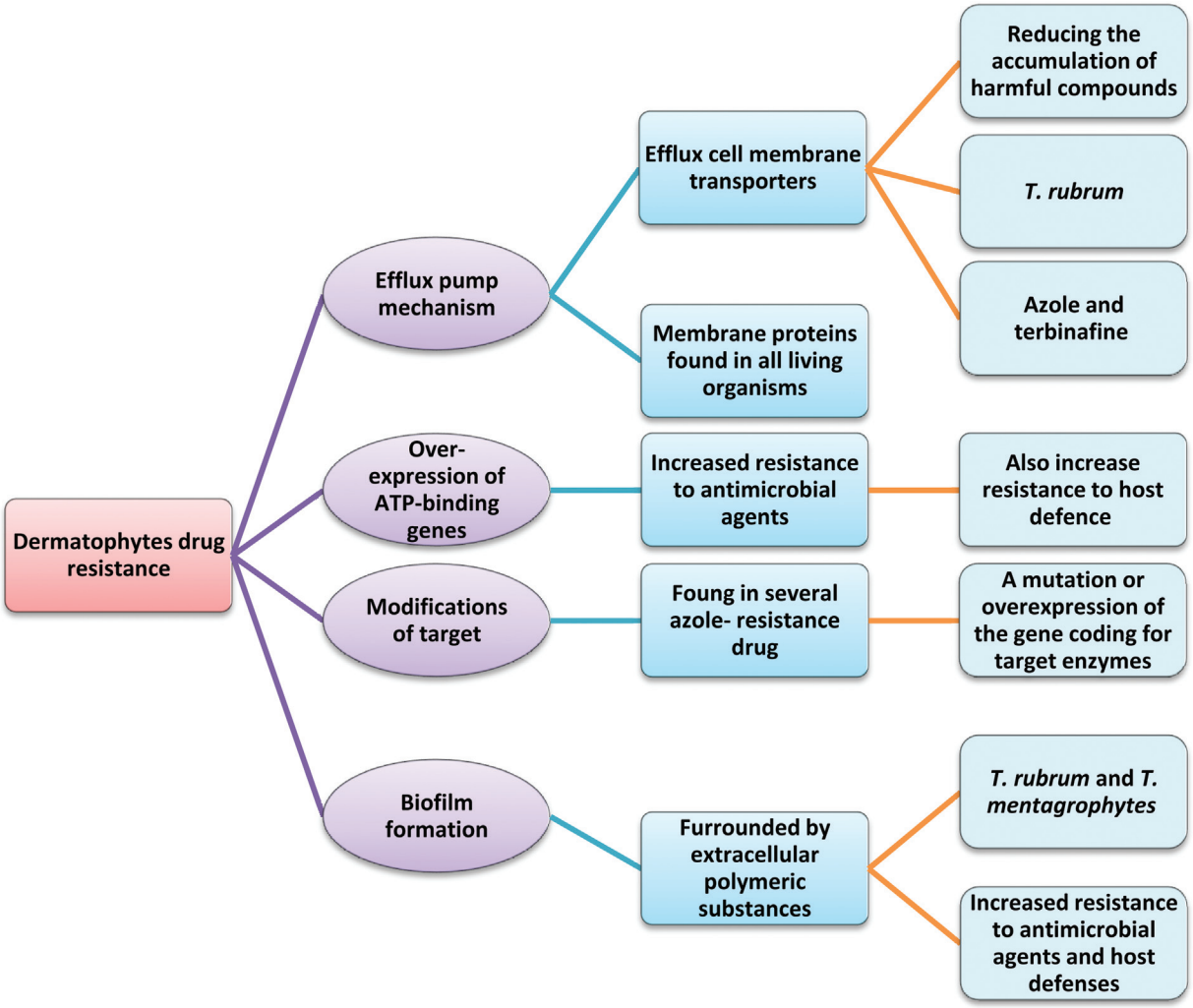
To discover new antifungal agents, we need a long time may be more than a decade, so existing drugs can give satisfying results regarding dermatophyte treatment when these drugs formed in other formulas was found to be effective. This may help add new antifungal drugs to manage dermatophytosis [22]. Since we have few numbers of antifungal agents available for dermatophyte infection, so new improved antifungal is required by modification of traditional drugs chemically or structurally [22]. Another important issue is combination of antifungal drugs to obtain the synergic action such as a combination of topical agents with anti-inflammatory drugs [17,22].

The major two antifungal drug classes to treat dermatophyte infection are azole as (tioconazole, clotrimazole, oxiconazole, econazole, miconazole) and allylamine as (terbinafine and naftifine). Terbinafine is the most common topical treatment of dermatophytosis [17]. There is no evidence regarding the superiority of one topical antifungal class over another drug with cure outcome at the end of management [27–30]. The natural sources considered promising branch for discovering a new antifungal agents by preparing modern compounds [31].

Investigating the antifungal activity of epigallocatechin 3-*O*-gallate (EGCg) and antifungal agents against 35 of dermatophytes clinically isolated have been studied. These activities of EGCg were approximately fourfold higher than those of fluconazole and were 4-fold to 16-fold higher than flucytosine. This result indicates that EGCg can inhibit pathogenic dermatophyte species [32].

Nine plant essential oils, were evaluated for their antidermatophytic properties. All essential oils were active against the dermatophyte. The minimum

Figure 1



Mechanisms actions of drug resistance in dermatophyte.

inhibitory concentration (MICs) recorded for the plant oils tested ranged from 0.25 to 4 mg/ml [33].

Recent revolutions and high prevalence rate of dermatophytosis

Through the past 20 years, the predominance of fungal infection significantly increased, due to many reasons, as an inappropriate way for medication administration [11]. Also a high prevalence of dermatophytosis can be seen in AIDS patients due to their weak immune system that makes them more susceptible to fungal infections [24].

There are about 100 000 species from millions of fungal species on the earth that can infect humans and animals, especially in tropical and temperate countries [1,34,35]. Dermatophytes are filamentous fungi naturally living on keratinous materials found in soil [7]. They include at least 40 different species which have some different morphological characters [1,36]

The predominance of dermatophytosis is about 20–25% of the total population of the worlds [1,2]. This disease causes chronic morbidity with a high prevalence distribution in the entire world [37,38]. It takes a different pattern of infection which reflects a variable geographic distribution [39]. The most favorite growth conditions for dermatophytes are moisture and warmth that are regarding as encouraging factors in tropical countries [11]. Other conditions required for dermatophyte growth and development are a low degree of hygiene, hot weather with physical activity, and increased sweating [40]. However, the epidemiology of such disease has changed due to lifestyle, migration, socioeconomic conditions, drug therapy, and immunosuppressive state [1,39].

T. rubrum is the predominant isolates from humans followed by *Trichophyton mentagrophytes* [41–44]. This is clear in Europe when a high incidence of *T. rubrum*

infection was recorded [1]. Traveling and migration have a crucial role in the prevalence of dermatophytosis, so new species or strains can be detected in any region in the world that never has been found before. The contagious nature of dermatophytosis makes it easy to spread from person to person or from animals to humans [1].

Prevalence and incidence of dermatophytosis can be enhanced by adaptation to be stored as spores in household dust for long years, the dust act as a reservoir [1]. Dermatophyte infections with chronic disorders have been observed clearly in the last few years, with increasing prevalence and incidence [18,45]; these chronic infections appeared difficult to treat [45]. At the present, dermatophytosis revealed a high recurrent infection that never seen before [46].

Long duration of treatment

Dermatophytosis treatment may require a longer period of weeks to months as in onychomycosis treatment [17]. Long duration of treatment is considered a problem associated with the use of any antifungal drugs [22].

Recovery in a short period from dermatophytosis became urgent issues because long-duration management is considered expensive and time losing, so development of antifungal agents with short duration is important to improve the quality of patient's life as well as considered additional reason to prevent emergence of dermatophyte-resistant strains due to long management that gives fungus chance to be resistant [11]. Quality of life of patients will be increased when new drugs are used to cure infectious lesions in a short time [22].

Side effects associated with dermatophyte agents

As with any antimicrobial drug, antifungal agents have adverse effects that have been reported [47–51]. Management of this infection became a true problem in some people groups as the elderly, children and pregnant women; adverse effects are unacceptable in these groups [52].

At present, information concerning systemic antifungal of dermatophytosis drugs during pregnancy is incomplete [52]. Serum absorption tends to be minimal with topical therapy [17]. So, topical antifungal drug is recommended in pregnant women because topical drugs are effective and safe with low risks compared with systemic antifungal agents [18,30]. It is worthy to mention that topical antifungal agents have no side effects when used during lactation [53]. Topical preparations are much less costly than orally administered antifungal drugs and cause minimal adverse side effects [54,55].

Some drugs such as allylamines and azole antifungal classes are utilized topically in pregnant women, children, and the elderly [52]. Systemic terbinafine are safe in the elderly because it lacks cardiac complications, while it must be stopped in lactation and pregnancy; however, all systemic antifungal drugs may best be avoided [52]. In pregnant women miconazole and clotrimazole are safe and first-line choice, while econazole must be avoided in the first trimester [19].

Dermatophyte infection recurrence

Recurrent dermatophytosis refers to the recurrence of the dermatophyte infection within a few weeks, after full completion of treatment [46]. The relapse has been noted with most types of dermatophyte infection [17]. Infection transmission from symptom-free carriers like family members and pets may need to be controlled with adjunct therapies and techniques; fomites such as hats and combs must also be treated. Patients must be encouraged to complete a full treatment cycle, as infection can be present without visible symptoms [17,46].

Recurrence infection was observed at the sixth week in 12.5% of completely treated patients with terbinafine [56]. Mycological recurrence has been recorded in 32% of cases treated with continuous terbinafine to manage onychomycosis [57]. After a long-term follow-up of onychomycosis treated with systemic terbinafine and itraconazole, researchers suggested that itraconazole therapy is more likely to produce mycological recurrence compared with terbinafine therapy [58].

Chronic or recurrence infection may be occurred due to the deposition of dermatophytes in the deep-seated lesions of the skin [59]. *T. rubrum* and *Trichophyton verrucosum* were implicated in forming deep-seated hyphae in a patient treated with immunosuppressant drugs for non-Hodgkin's lymphoma. Spores were found in skin biopsy specimens [60].

Deep dermatophytosis is a severe and sometimes life-threatening fungal infection caused by dermatophyte. Deep dermatophytosis in 17 patients with no known immunodeficiency have been reported, four patients died, no other severe infections, fungal or otherwise, were detected in those patients [61]. Apparent distress to the patients socially, financially, and emotionally are

occurred due to recurrent and chronic dermatophytosis [46].

The incomplete course of management and an inappropriate dose of antifungal drugs are considered important factors for the emergence of resistant strains and recurrence of infection that may become predominant among peoples [44]. However, recurrence of dermatophytosis is the most serious problem that should be considered after completing the curative time (within 4 weeks of stopping therapy) [17,18]. It could be resulted from recontact with the source of infection or from failed treatment with antifungal drugs [44].

Relapse of dermatophytosis is also detected in patients after 1–4 weeks of treatment with clotrimazole cream [62]. However, factors such as depth of lesions and even socioeconomic conditions may be responsible for the recurrence of dermatophytosis infection [59,63]. Recurrence of dermatophytosis is predominant among Indian patients with tinea pedis [64]. However, another study in India found more frequent relapse in patients with tinea cruris and tinea corporis [63].

Zoophilic nature of dermatophytes

Dermatophytosis can be developed in both humans and animals with some differences in clinical features [12–14,65]. The zoophilic group of dermatophytes is the most causative agents of dermatophytosis in humans and animals. Zoophilic lesion is considered more progressive than lesions caused by another dermatophyte that is transmitted from person to person without animal transmission as the anthropophilic type [65]. Otherwise, humans can become a source for infection to wild animals as noted in the laboratory or other workplaces [13].

Humans can easily get dermatophyte infection from contact with different types of animals such as cats, dogs, Guinea pigs, and rabbits [1,66]. Small pet animals are capable of transmission of infections to humans, especially to children because animals are more association with our life recently [67].

Dermatophyte infection can be transmitted by wild animals, laboratory animals, and farm animals, sometimes it is workplace-related diseases [13]. The most frequent zoophilic dermatophytes are *Microsporum canis* and *T. mentagrophytes* [65,68–71]. Some animals may be considered a carrier of dermatophyte without showing any signs of infection that can spread to humans [13,67].

Physiological processes are similar between fungi and humans

Production of the new antifungal drug is a challenge to the researchers due to high similarities in the cell structure of both humans and fungi, the most common antifungal agent's target include fungal cell membrane compounds, fungal nucleic acid, and components of a fungal cell wall [22]. So, new targets must be focused by researchers by learning more about the mechanism of action of antifungal drugs and fungal pathogenesis.

Incorrect diagnosis and differentiation of dermatophyte infection

Owing to the wide range of fungal species with numerous morphological features, mycological investigation is considered so important for the diagnosis of these fungal species [72]. A lesion of tinea can be caused by a single species of dermatophyte or by many species in some cases [73]. Additionally, a single species of dermatophyte can caused different types of tinea [40]. The investigation for these fungi is very important in differentiation from other clinical skin diseases [70].

Clinical features such as itching, maceration, pain, scaling, vesicles, plaster forming, and erythematous rate are variable from mild to a moderate degree [37,74,75]. These signs may be confused with other diseases as contact dermatitis, bacterial folliculitis, psoriasis, and eczema. An incorrect diagnosis can be seen in suboptimal therapy, immunosuppressant persons, and inappropriate dose duration [46]. False-negative culture is considered a truly confusing matter because the infection cannot be recognized as new or relapse infections causing limitation in drug administration [22].

Few studies *in vivo* to test new drugs

In spite of the high prevalence of dermatophytosis, few investigations were implemented regarding dermatophyte infection as well as most consideration and studies were in-vitro investigations. Animal model in-vivo experiments can increase our information about the host immune response and the pathogenesis of dermatophyte. Also animal model is considered a promising way to evaluate modern antifungal agents against dermatophyte infections [15].

Because of lack of accurate testing outcome that correlates between *in vivo* and *in vitro*, the clinical outcome is considered a poor predictor when organisms are susceptibility testing *in vitro* under certain growth conditions, while they are resistant *in*

vivo [19]. Reproduction of human pathophysiology *in vitro* is difficult, so investigations using animal model in-vivo experiments are necessary [76].

There are always differences between the results of in-vitro and in-vivo experiments. These differences may be related to either to the host conditions, such as immune response, site of infection, and underlying illness, the fungal characters such as fungal virulence, or the antifungal agent, such as dose, pharmacodynamics, pharmacokinetics, and drug interaction [19].

No human vaccine is available

In spite of the fact that the prevalence of superficial mycotic infection worldwide is 20–25% of which dermatophyte are the most common agents [45], vaccines remain unavailable for humans at this moment.

Cell-mediated immune responses are important to develop resolution and protection for dermatophytosis presented by some cytokines such as gamma interferon, interleukin-12, and interleukin-2 [77,78]. There is no correlation between antibody titer and the severity of dermatophyte infections that has been reported [77]. Despite the availability of effective vaccines for certain animal species, vaccination against dermatophytosis requires improvement and further development in both animals and humans. Numerous dermatophyte virulence factors have recently been recognized; notably, secreted proteases have been involved in the invasion of the keratin network. Their precise roles in the different steps of the infectious process and immunopathogenesis are being studied, while all aspects of the host immune response against dermatophytes, including the innate response, are becoming increasingly documented [79].

Inactivated *M. canis* vaccine has been used to treat cats infected with dermatophytosis; it was effective and safe against infection caused by *M. canis* [80]. Moreover, inactivated vaccine such as 'Funhikanifel' was used for the vaccination of dogs and cats [81]. Inactivated fungal vaccine has been used as a successful therapy to treat infected cats with dermatophytosis by accelerating healing of the lesions [82].

The clinical investigation suggested that a vaccination for a single dermatophyte species can be followed by wide-based immunity to different skin antigens. Rabbits immunized with a single dermatophyte as *M. canis* is capable of developing delayed-type hypersensitivity to other antigens as *T. mentagrophytes and M. gypseum*. Also Guinea pigs already vaccinated with *T. equinum* developed protection against *M. canis* [83].

Strategies and future steps to resolve dermatophyte treatment problems

At present, antimicrobial resistance became common [84–87]. Due to few antifungal drugs available to treat dermatophyte infections, some strategies must become the focus of attention as traditional drug modification, developing modern formulas of antifungal agents, and antifungal drug combinations to get synergic action against dermatophytosis.

Photodynamic and laser therapy are focusing attention now to treat dermatophyte infections [18,83], this branch of treatment needs more studies regarding the optimal effective dose and duration. The natural sources considered promising branch for discovering new antifungal agents by preparing modern compounds with new drug mechanisms [31].

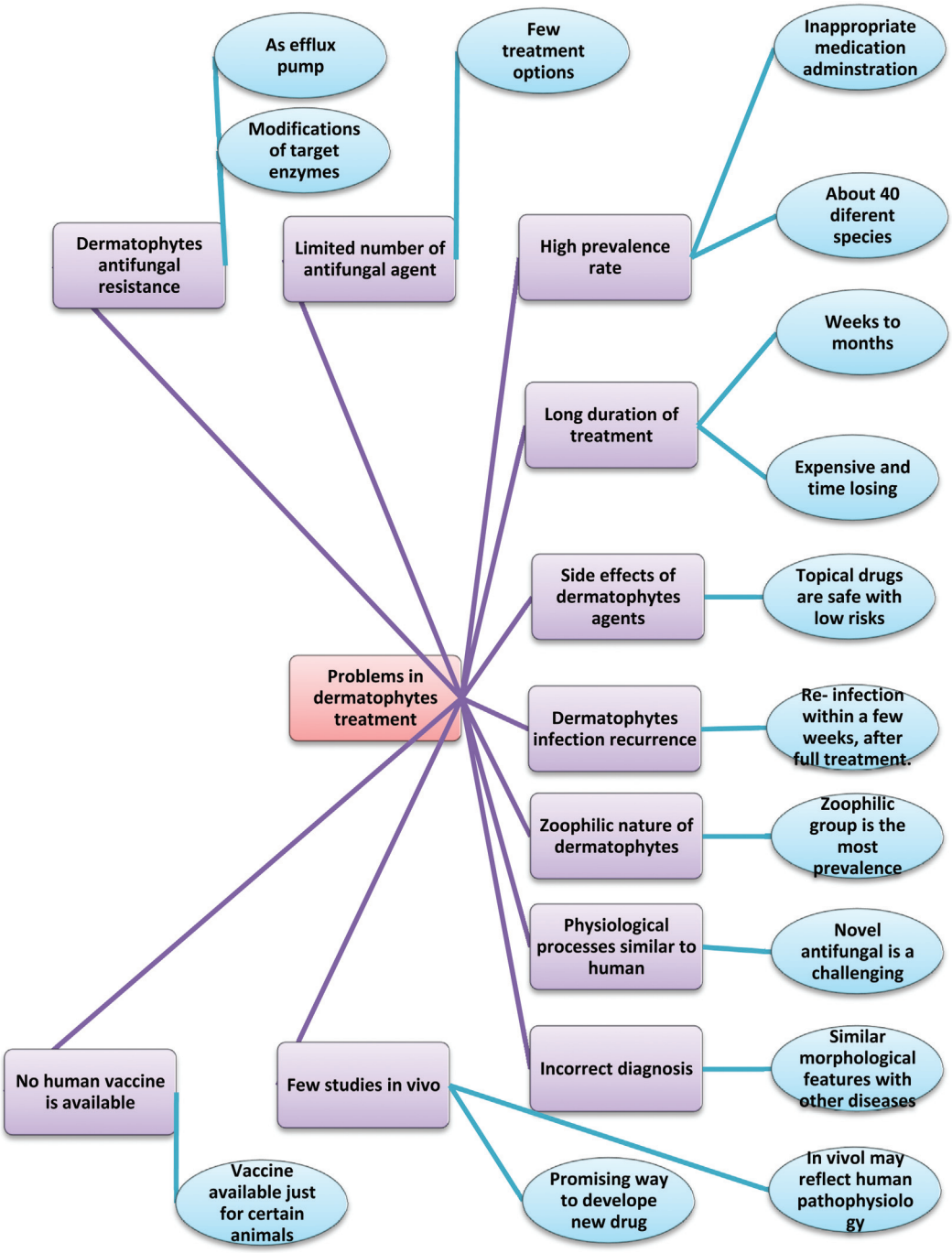
Due to the few antifungal drugs available to treat dermatophyte infections, some strategies must become the focus of attention as traditional drug modification, developing modern formulas of antifungal agents and antifungal drug combinations to get synergic action against dermatophytosis.

Antifungal agent resistance can be enhanced by recurrent dermatophytic infections that lead to emergence new strains resistant to traditional antifungal drugs, so preventing recurrence of infection is a fundamental step to prevent drug resistance [46]. More studies regarding topical treatment are required because topical preparations are much less costly than orally administered antifungal drugs and cause minimal adverse side effects [88–92] (Fig. 2).

Conclusion

Dermatophytosis is considered a prevalent skin disease worldwide; it occurs in both humans and animals. The major challenges and problems in dermatophytosis treatment for clinicians and researchers are dermatophyte antifungal resistance, the limited number and availability of antifungal agents, high prevalence rate and revolutions of dermatophyte recently, and long duration of treatment. The side effects of antifungal agents, dermatophyte infection recurrence, zoophilic nature of dermatophyte, similar physiological processes between fungi and humans, incorrect diagnosis and differentiation of dermatophyte infection, few studies

Figure 2



Major problems in dermatophytosis treatment.

in vivo to test new drugs, and no human vaccine available are further challenges.

Learning more regarding the reasons for treatment failure is so important an issue to be studied because few researches in this branch are available at present. Discovering new drugs or modification of old ones will participate to increase the limited number of antifungal drugs. Topical therapy has the advantage of safety with very few side effects, used without laboratory monitoring, much less costly, easy to use, do not require hospital visiting, and safe in lactation. So this branch is important to be developed. Incorrect diagnosis represents a challenge in dermatophytosis treatment such as difficulty in differentiation of dermatophyte infection from other similar manifestations by clinicians, and laboratory incorrect diagnoses such as false negative results.

Human vaccine availability against dermatophytosis is demanded, especially for people with high risk of

infection with dermatophytes. Vaccine therapy is a promising idea instead of a conventional limited number of antifungal drugs, so focusing on this issue is promising. Appropriate vaccines for dermatophyte infection may need a deep understanding of the basic immune mechanisms of the host.

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Conflicts of interest
There are no conflicts of interest.

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