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Review article

Antifungal agents and their action against dermatophytes: curious to know the facts

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Abstract

Despite the improvement of antifungal therapies over the last 30 years, the development of antifungal resistance continues to be the major concern in clinical applications. Within 10 years the molecular mechanisms underlying this development were extensively unraveled. In this paper, a short summary of presently accessible antifungal, and their action against dermatophytes are elaborated. It seems that major mechanisms of resistance are essentially attributable to the release of antifungal resistance effectors genes. This release could be the consequence of point mutations occurring in transcriptional regulators of these effectors genes. Resistance may also follow the emergence of point mutations directly within the genes coding antifungal targets. Additionally, we tend to describe new possible ways, presently undertaken to discover various medical therapy targets and antifungal. Identification of new antifungal is achieved by a screening of natural or synthetic chemical compound collections. Discovery of new reputed antifungal targets performed through genome-wide approaches for much better understanding of the human pathogenic fungi biology. In this review, we will discuss different antifungal agents and their mechanism of action.

Introduction

The fungal kingdom encompasses a massive diversity of taxa with varied ecological niches, life-cycle methods, and morphologies. However, a little-known fact is true biodiversity of Kingdom Fungi. Of the 1.5 million species estimated to belong to this present kingdom solely 5% are formally classified. Several fungi are parasites for plants, animals, human, and other different fungi. Plant infective fungi are able to cause harm and losses to agriculture and forestry together with the rice blast fungus, Dutch elm disease, and chestnut blight. Some different fungi may cause serious diseases in humans, many of which can be fatal if left untreated.The so-called Dermatophytic and Keratinophilic fungi will attack eyes, nails, hair, and particularly skin and cause native infections such as ringworm and athlete's foot. Fungal spores are also a reason for allergies and fungi from different taxonomic groups that can provoke allergic reactions. In this paper, antifungal agents and their action were detailed.

Fungal Infections, Clinical Treatments, and Incidence of Antifungal Drug Resistance

Fungal Infections

At the start of the 20th century, microorganism epidemics were a worldwide and vital reason behind mortality. In distinction, fungal infections were nearly not under consideration. Since the late 1960s once antibiotic therapies were developed, a forceful rise in fungal infections was determined, and that they presently represent a worldwide health threat. The growing number of immuno-deficient cases related to AIDS, cancer, old age, diabetes, cystic fibrosis, and organ transplants and other invasive surgical procedures influences this increasing incidence of infection.

It is also necessary to notice that fungal infections are often classified in function of the tissue infected (table 1). Cutaneous and subcutaneous mycoses caused by dermatophytes fungi that affect-keratinized structures of the body. The most concerned dermatophyte genera involved are Trichophyton, Epidermophyton, and Microsporum. In most cases, cutaneous fungal infections need a challenge of an immune system, and their incidence varies depending on the site of infection. For instance, onychomycoses are very

frequent in the worldwide population, with an incidence varying from 5 to 25% [1].

Biochemical Targets for Antifungal Chemotherapy

Fungal cells are complicated organisms that share many biochemical targets with different eukaryotic cells. Consequently, agents that interact with fungal targets no longer observed in eukaryotic cells. The fungal cellular wall is a unique organelle that fulfils the standards for selective toxicity. The fungal cell wall differs greatly from the bacterial cell wall and isn't always affected by antibacterial cell wall inhibitors such as the β-lactams or vancomycin [2]. The arrangement of the bimolecular components of the cell wall accounts for the individual identity of the organism. Despite the fact that, each organism has a different biochemical composition, their gross cell wall structure is similar. There are three general mechanisms of action for the antifungal agents: cell membrane disruption, inhibition of cell division and inhibition of cell wall formation [4].

Inhibition of Cell Wall Formation

Interference with fungal cell wall biosynthesis has no longer been successful and effective as penicillin and cephalosporins against bacteria. Many chemicals substances were discovered that interfere with various steps in fungal cell wall synthesis with great antifungal activity *in vitro*. Unfortunately, development of these agents into useful drugs has proven has verified very difficult. Many of these agents developed to target β-glucan synthesis [5].

Table 1. Characteristics of main fungal infections worldwide.

Body location	Pathogen type	Organ	Most frequent genus	Estimated incidence of infection
Superficial	Primary	Skin and hairs	Malassezia	~140,000,000 cases/year
Cutaneous	Primary	Skin and nails	Trichophyton Epidermophyton Microsporum	~150,000,000 cases/year

* adapted from "The Fungal Research Trust. How common are fungal diseases? Fungal Research Trust 20th Anniversary meeting. London June 18th, 2011.

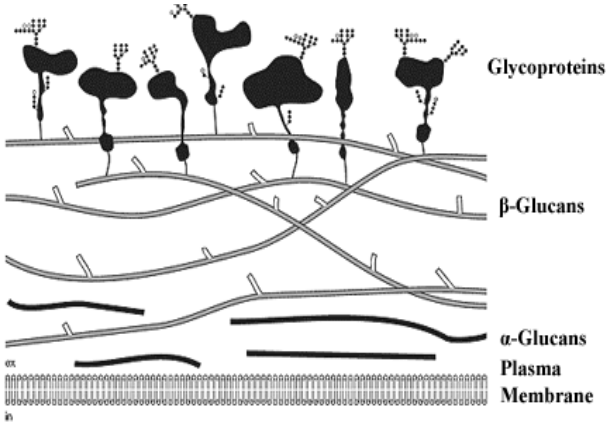

Figure 1. Structure of plasma membrane [3]

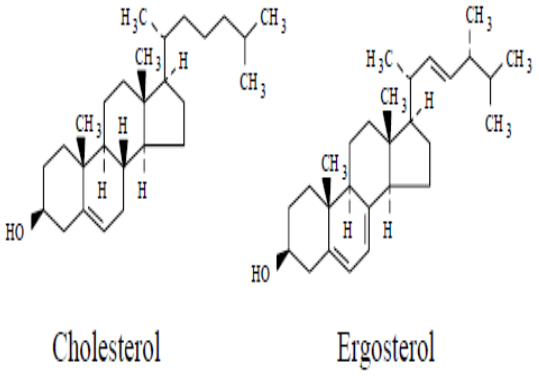

Figure 2. Chemical structure of Cholesterol and Ergosterol [7]

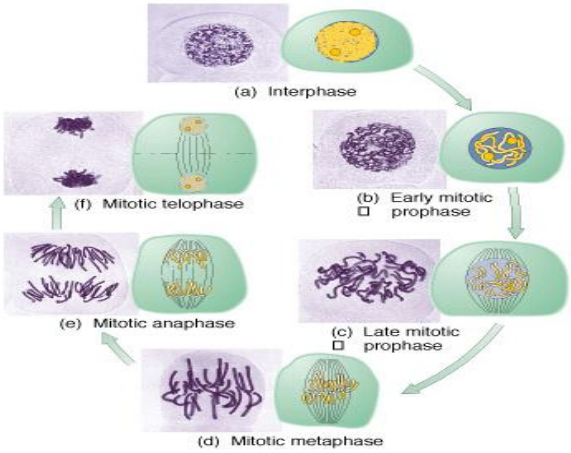

Figure 3. Mitotic Spindle [8]

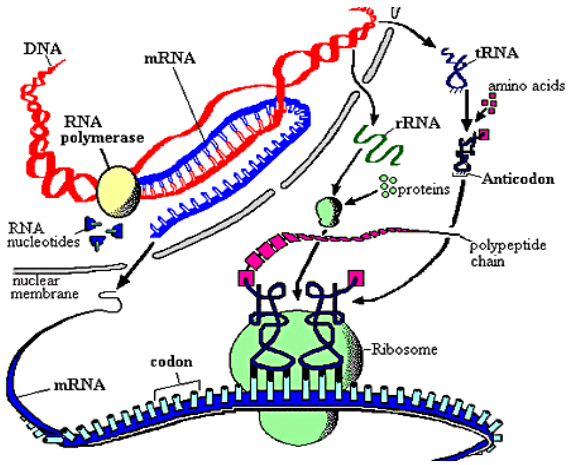

Figure 4. DNA transcription [8]

Cell Membrane Disruption

Antifungal agents that disrupt the cell membrane accomplished by targeting ergosterol, either by binding to the sterol, forming pores and causing the membrane to become leaky (as with polyene antifungals), or inhibiting ergosterol biosynthesis. Ergosterol is similar to mammalian cholesterol; hence, agents binding ergosterol may also have a cytotoxic effect in the host tissue. Ergosterol has two conjugated double bonds that might be lacking in mammalian sterols [6]

Antifungal Agents

Despite good research dedicated to the development of recent therapeutic techniques, there are only a limited number of available drugs to fight against invasive fungal infections [9]. Certainly, only four molecular classes that target on three distinct fungal metabolic pathways presently used in clinical practice to treat essentially systemic fungal infections: fluoropyrimidine analogues, polyenes, azoles, and echinocandins. Numerous different classes, such as morpholines and allylamines are only used as topical agents due to either bad efficacy or excessive adverse effects whilst administered systemically [9].

Griseofulvin

Griseofulvinis an antifungal made from *Penicillium griseofulvin*. The therapies must continue until new tissue replaces the old diseased tissue. When given orally, plasma-borne griseofulvin becomes integrated into keratin precursor cells and ultimately into keratin that cannot help fungal growth [10]. The structure is shown in figure 5.

Mechanism of Action: Griseofulvin inhibits microtubule polymerization hence, inhibiting the formation of the mitotic spindle.

Adverse effects: A headache is a common adverse effect. It may cause aplastic anaemia. It is being gradually replaced by newer agents.
Products: Fulvicin-U/F, Griseofulvin V, Gris-PEG

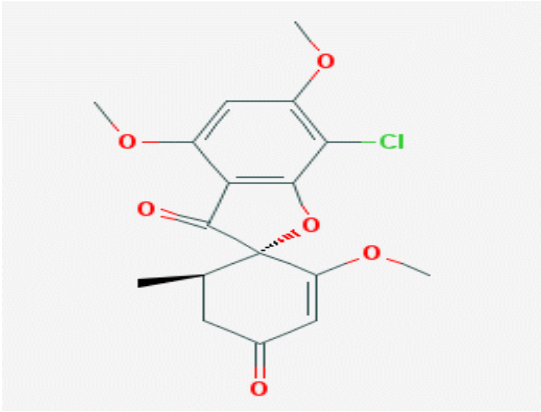

Figure 5. Chemical structure of Griseofulvin [11]

Ketoconazole

Ketoconazole (figure 6) is produced as a cream or in shampoos format with a one- or two-percent, for the treatment of tinea pedis, tinea corporis, tinea cruris and cutaneous candidiasis. The adverse effects include itching, stinging, skin rash, dry skin, and dry or oily scalp. Products: Nizoral Cream, Nizoral A-D Shampoo (1%), Nizoral Shampoo (2%).
In 1981, the Food and Drug Administration (FDA) approved brand a new antifungal, ketoconazole, developed by Heeres and his co-workers [13]. This drug became the best antifungal available for treatment of systemic fungal infections caused by yeasts for the following 10 years. However, there are many drawbacks to this drug. It is poorly absorbed when administered orally, and no ketoconazole form has ever been advanced for intravenous injection. Furthermore, it cannot pass the cerebrospinal barrier and is less active in immune-suppressed patients [14-16]. It causes a few severe side effects consisting of a decrease in testosterone, glucocorticoids production and liver and gastrointestinal complications [17, 18]. Finally, several interactions with other drugs were defined. For these reasons, the triazoles were developed.

Fluconazole

Fluconazole is a once-a-day tablet or suspension to treat yeast infections of the vagina, mouth, throat, esophagus, abdomen, lungs, blood and other organs. Fluconazole is also used to treat meningitis and might prevent yeast infections in patients who are prone to infection because of chemotherapy or radiation therapy, before bone marrow transplants. Some adverse effects include a headache, dizziness, diarrhoea, stomach pain, heartburn and changes in the capacity to taste food. Side effects that are more effective can include excessive tiredness, loss of appetite, upset stomach, vomiting, tingling or numbness in the extremities, fever, chills, rash, hives and difficulty in breathing or swallowing. Hepatoxicity includes yellowing of the eyes or skin, dark urine or pale stools.

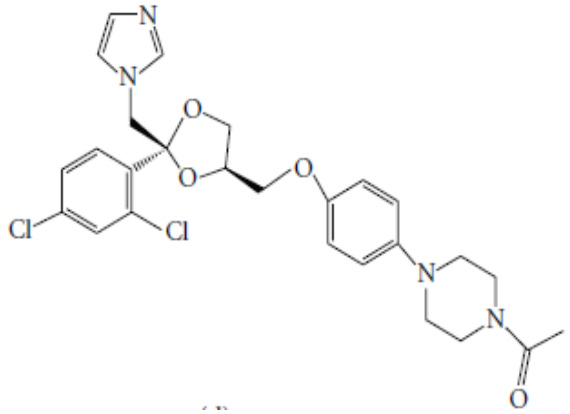

Figure 6. Chemical structure of Ketoconazole [12]

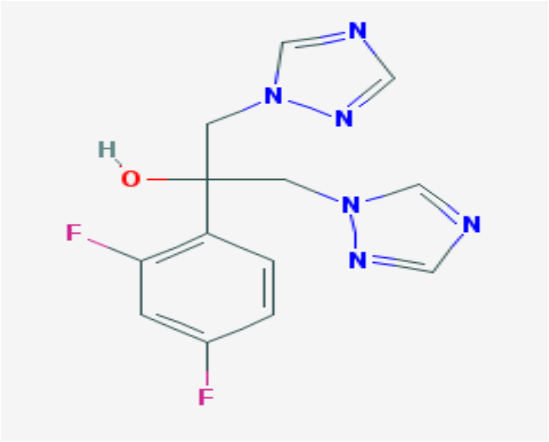

Figure 7. Chemical structure of Fluconazole [20]

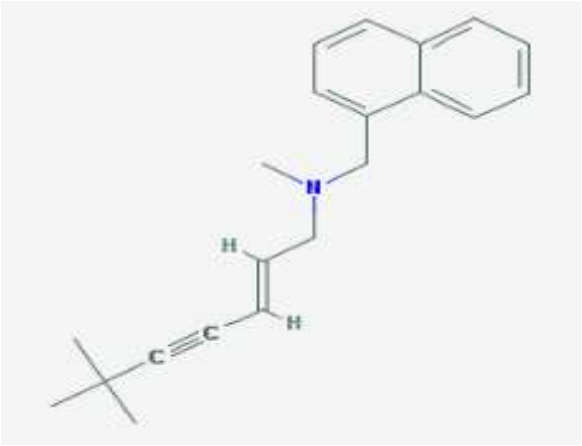

Figure 8. Chemical structure of Terbinafine [21]

Fluconazole (figure 7) were available for use by clinicians in 1990 and provided several advantages over the use of imidazoles. Fluconazole is highly hydrosoluble and therefore can be easily injected intravenously. It is completely absorbed through the gastrointestinal tract, and it diffuses throughout the whole body, including cerebrospinal fluid [19]. Because of its excellent pharmacokinetic properties as well as its broad spectrum of activity, fluconazole was the gold-standard remedy for fungal infections during the 1990s. Regrettably, the over prescription of this drug with the aid of physicians for prophylaxis or treatment led to an increase in resistance to azole drugs.

Terbinafine

Terbinafine has been evolved as a new class of ergosterol biosynthetic inhibitors which can be functionally in addition to chemically distinct from the other major classes of ergosterol- inhibiting antifungal agents [18]. Terbinafine (figure 8) is extensively effective against dermatophytes *in vivo* and *in vitro*. A recent study of terbinafine via the research studies investigating the efficacy of this agent against disseminated candidiasis in an animal model are under way.

Itraconazole

Itraconazole were approved and made available by the FDA in 1992. This triazole possesses a vast spectrum of activity throughout fungal species comparable to this of ketoconazole and wider than fluconazole treatment of histoplasmosis, blastomycosis, and paracoccidioidomycosis. However, itraconazole is hydrophobic and is more toxic than fluconazole. Itraconazole is restricted and indicated for the treatment of onychomycosis, of superficial infections, and in some cases for systemic aspergillosis [22]. An injectable formulation of itraconazole was made available in 2001 [23].

Prevention and Control of Antifungal resistance

New strategies and techniques to avoid and to suppress the emergence of antifungal resistance have no longer been defined.

However, approaches analogous to the ones recommended for antibacterial [24-26] may be suggested. These measures consists (i) prudent use of antifungal, (ii) appropriate dosing with unique emphasis on avoiding treatment with low antifungal dosage, (iii) therapy with combinations of present agents, (iv) treatment with the appropriate antifungal (in cases where the etiological agent is known), and (v) use of surveillance studies to determine the true frequency of antifungal resistance. It has to further emphasize that data supporting the use of the suggested measures is largely lacking, and ongoing studies may provide some additional specific guidelines in the near future. Additionally, advances in the rapid diagnosis of fungi can be beneficial in lowering the use of inappropriate anti-fungals to treat organisms, which are resistant to a particular agent. Unfortunately, developing the diagnostic methods specific to fungi has been slow. The recent approval of a reference technique for the antifungal susceptibility testing of [27] is encouraging and gives a possible way for performing surveillance studies.

Table 2. Mechanism of action of drugs

Drug	Action
Griseofulvin	Antimitotic via microtubule Inhibition
Ketaconazole	Blocks ergosterol synthesis via P450 inhibition (not selective)
Itraconazole	Selective block of ergosterol
Fluconazole	Selective block of ergosterol
Terbinafine	Inhibits squalene metabolism - squalene is toxic; also blocks Ergosterol

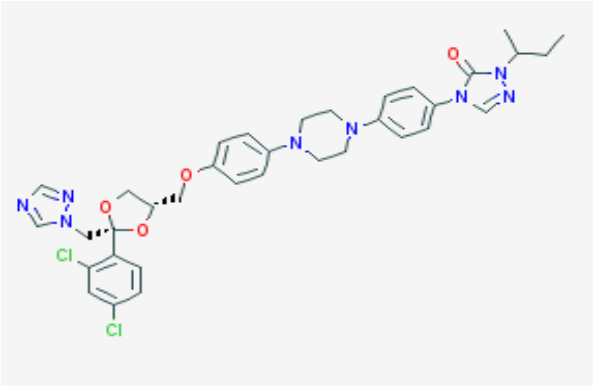

Figure 9. Chemical structure of Itraconazole

Conclusion

The expression of resistance to antimicrobial agents is the logical and inevitable result of usage of these agents to treat human infections. The availability of molecular genetics tools has brought a rapid expansion in our understanding of the mechanisms by using which antibacterial resistance emerges, spreads, and promises greatly informs efforts to develop novel and effective compounds for future use. With elevated use and availability of different classes of antifungal agents, that anticipates with an increasing number and numerous fungal species resistant to these agents. Continuous efforts to study the mechanisms of antifungal resistance and the improvement of experimental systems (similar to those available in bacteria) in which individual resistance mechanisms can be studied might be important components of a strategy to limit the emergence of resistance to these agents and to develop safer and more potent compounds for the future.

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