Disruption of fungi cell membranes by polyenes, azoles, allylamines, amino acids and peptides

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ABSTRACT

The fungal cell membrane is one of the targets for some groups of antifungal agents: the polyenes, lipodepsinonapeptides, amino acids and other peptides, which interferes with the structural integrity of the lipid bilayer. Polyene antifungals show effectiveness against sterol-containing organisms by interacting directly with the fungal ergosterol. Amphotericin B exhibits activity against most species of Candida, Cryptococcus neoformans, most Aspergillus sp., hyaline molds, Penicillium, Paecilomyces, and Scopulariopsis, dimorphic fungi including Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, and Paracoccidioides brasiliensis. Nystatin binds to sterols in the cell membrane of yeasts resulting in electrolyte leakages. Statins are competitive inhibitors of HMG-CoA reductase, which is involved in the ergosterol synthesis. The azoles specifically inhibits the cytochrome P450 enzyme CYP51, resulting in interruption of membrane synthesis, depletion of ergosterol leading to an increase in toxic methylated sterol precursors in the cell membrane. The morpholines are synthetic antifungals and inhibits the reductase and isomerase enzymes in ergosterol biosynthesis triggering accumulation of dimethyl-lanosterol and depletion of ergosterol. Aureobasidins are highly lipophilic and act by inhibiting inositol phosphoceramide (IPC) synthase, critical in fungal sphingolipid biosynthesis thereby depleting essential sphingolipids in the fungal cells. The lipopeptide iturin acts by increasing membrane permeabilization in fungal cell. Lipodepsinonapeptides produced by Pseudomonas syringae interacts with the fungal cell membrane by pore formation resulting in fatal electrolytic leakage. Syringomycins form ion channels in the fungal plasma membrane employing a novel sphingolipid-modulated channel formation mechanism while Pseudomycin A alters several membrane functions like membrane potential, protein phosphorylation, H1-ATPase activity, and cation transport fluxes.

Keywords: Antifungal, azoles, cell membrane, ergosterol, polyenes.

INTRODUCTION

Fungi have fundamental functions in terrestrial ecosystems, in degradation of organic matter and in nutrient uptake of plants through mycorrhizal interactions. Fungi are achlorophyllous, non-motile, eukaryotic organisms with bodies (thalli) composed of elongating walled filaments (hyphae). They have a chitinous rigid cell wall as well as various polysaccharides (1, 4- and α 1, 6-glucans) and an ergosterol containing cell membrane (Kwon-Chong and
Bennett, 1992; Chapman et al., 2008). They are heterotrophs, requiring external sources of carbon for energy and cellular synthesis and have adopted three different trophic strategies to obtain this carbon, occurring as saprotrophs, necrotrophs, and biotrophs (Finlay, 2008). An antifungal agent is a drug that selectively eliminates fungal pathogens from a host with minimal toxicity to the host (Baron, 1996). The three major groups of antifungal agents in clinical use are the azoles, polyenes, and allylamines/thiocarbamates, with their antifungal activities based on inhibition of ergosterol synthesis, the predominant component of the fungal cell membrane (Parks and Casey, 1996).

Antifungal agents early discovered and used included the potassium iodide (KI), weak acids, phenol, dyes as well as the oils (Mercurio and Ewelski, 1993). The success obtained from their therapeutic use was however limited until saturated solution of Potassium Iodide (SSKI), was demonstrated to be active against cutaneous sporotrichosis although the agent had narrow spectrum (Mercurio and Ewelski, 1993). The first landmarks recorded in antifungal therapy was the discovery of Griseofulvin in 1939 (Oxford, 1939; Sheehan et al., 1999), 1944 discovery by Wooley of the first azole, benzimidazole (Wooley, 1944); 1945 report on the fungistatic activity by Elson (1945). Also there was the discovery of the first Polype vacrulide antifungal (Nystatin) in 1950 which defined modern antifungal era (Hazen and Brown, 1950; 1951). The challenge however was the toxicity of these early antifungals to human cells. Ergosterol, the major sterol in fungal cell membranes, is of great importance for membrane fluidity (Bowman et al., 1987). This provides the basis for two types of selective antifungals, the polyenes, which interact directly with ergosterol in the membrane, and compounds inhibiting different steps in ergosterol biosynthesis e.g. azoles, allylamines, thiocarbamates and morpholine derivatives (Gooday, 1995). Gale et al. (1975) and Kerridge et al. (1976) showed that the stationary-phase of Candida cells were more resistant to the polye that at those the exponential-phase. This observation was attributed to the fact that in the exponential-phase cells, breakdown and re-synthesis of cell wall constituents occurs at a high rate, resulting in improved polye access to the cell membra. In contrast, the stationary-phase cells would be expected to break down and synthesize cell wall at a much lower rate (Kerridge et al., 1976). Also, the fatty acyl composition of membrane phospholipids influences the toxicity of polye as alteration in the ratio of various phospholipids may affect the internal viscosity and molecular motion of lipids within the membrane (Abu-Eiteen and Hamad, 2011).

**Amphotericin B**

Amphotericin B alongside amphotericin A is a polye antifungal produced by the soil actinomycete Streptomyces nodosus and displays activity against organisms with sterol-containing cell membranes (Ghannoum and Rice, 1999). Initially, it was the first line antifungal for aspergillosis but over the years, its first line use has been reduced though it is still a preferred drug for most fungal infections (Hall, 2012). It exhibits broad spectrum activity against most fungi including most species of Candida (Rodriguez-Tudela et al., 2009), Cryptococcus neoformans, most Aspergillus sp. (Barry et al., 2000), hyaline molds, including most species of Penicillium, Paecilomyces, and Scopulariopsis, dimorphic fungi including Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, and Paracoccidioides brasiliensis (Hall, 2012). Amphotericin binds to ergosterol in cell wall membrane of fungi, resulting in alteration of membrane permeability by forming oligodendromes that function as pores through which there is a leakage of cellular contents (Park et al., 2006). Although amphotericin B has a greater affinity for the fungal ergosterol, it also has some affinity for binding to the cholesterol of mammalian cell membranes (Abu-Salah, 1996). Also, the pore formation with ergosterol has a 100-fold longer half-life than pores formed after binding cholesterol (Bruty and McPhie, 1996). The drug demonstrates a concentration-dependent activity with a long post-antifungal effect (Andes, 2003).

**Polyenes**

The discovery of nystatin (fungicidin; C₁₂H₁₇NO₁₇) and amphotericin B (AMB or fungizone; C₄₁H₇₂NO₁₄) in the 1950s has led to the isolation and characterization of numerous antimicrobial agents (Abu-Eiteen and Hamad, 2011). Polye antifungals were developed from the fermentation of Streptomyces (Whiffen et al., 1946). Polye antifungals show effectiveness against organisms with sterol-containing cell membranes (e.g., yeast, algae, and protozoa). Ergosterol, the major sterol in fungal cell membranes but not found in other eukaryotic membranes, is of great importance for membrane fluidity (Bowman et al., 1987). Polye have large macrolide ring consisting of 12–37 carbon atoms closed by an internal ester of lactone and 6–14 hydroxyl groups distributed at alternate carbon atoms along the ring. Their uniqueness to fungal cells provide the basis for the activity of the group of selective antifungals, the polyenes, which interact directly with ergosterol in the membrane rather than the cholesterol of human cell membranes (Nosanchuk, 2006), as well as other compounds inhibiting different steps in ergosterol biosynthesis e.g. azoles, allylamines, thiocarbamates and morpholine derivatives (Gooday, 1995). Polyene antifungals were developed from the fermentation of Streptomyces (Whiffen et al., 1946). Polyene antifungals were developed from the fermentation of Streptomyces (Whiffen et al., 1946).
There is also evidence to suggest that amphotericin B-mediated cell killing may be due in part to the oxidizing properties of the drug that results in the production of reactive oxygen species and lipid peroxidation of fungal cell membrane (Brajtburg et al., 1990).

Nystatin is a polyene antifungal agent, obtained from Streptomyces noursei commonly used for the treatment of oral and vaginal candidiasis and is the first successful antifungal agent in therapy. Nystatin has shown activity against most yeasts, including Candida albicans, C. parapsilosis, C. tropicalis, C. guilliermondii, C. krusei, C. glabrata and also against dermatophytes including Trichophyton rubrum and T. mentagrophytes. Nystatin binds to sterols in the cell membrane of yeasts thereby increasing the membrane permeability which allow the release of K⁺, sugars and metabolites (Andes, 2003). Disruption of the cell membrane is believed to be responsible for fungal death, but modes of action of amphotericin B and nystatin have differences. Liposomal nystatin is a multimolecular liposomal formulation of nystatin, which contains nystatin, dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol in a ratio of 1:7:3 (by weight) (Dismukes et al., 2003). Nystatin has broad antifungal activity and is effective in vitro against most clinically important yeast and mold isolates (Mehta et al., 1987; Johnson et al., 1998; Oakley et al., 1999; Quindós et al., 2000; Arikan et al., 2002.)

Statins are competitive inhibitors of HMG-CoA reductase, which catalyze the conversion of HMG-CoA to mevalonate, a rate-limiting step in the isoprenoid biosynthetic pathway, which is involved in the synthesis of cholesterol in humans and ergosterol in fungi (Stancu and Sima, 2001). Statins compete with the natural substrate for the enzyme’s active site, preventing the formation of a functional enzyme structure with reversible binding (Corsini et al., 1999). Thus, the effects of statins are connected with the inhibition of the synthesis of important isoprenoids, e.g. farnesyl pyrophosphate and geranylglyceranyl pyrophosphate, which are important lipid attachments for the γ subunit of heterotrimeric G-proteins (Liao and Laufs, 2005) and guanosine triphosphate binding proteins (Liao, 2002; Ghittoni et al., 2005). Therefore, statins act as inhibitors of some G-protein actions and Ras or Ras-like signaling, which affect several important bioprocesses (Cordle et al., 2005). The growth inhibition effect of statins on yeast cells is related to the decreasing ergosterol level, which occurs because of the inactivation of HMG-CoA reductase inactivation by statins in the isoprenoid biosynthetic pathway (Sun and Singh, 2009). Ergosterol is a main constituent of the lipid layer of fungal plasma membrane and the antifungal effect might arise from decreased membrane fluidity in the yeast cells (Gyetvai et al., 2006). This assumption is confirmed by the observation that supplementation with ergosterol or cholesterol reduced the antifungal effect of statins, (Lorenz and Park, 1990; Macreadie et al., 2006). Lovastatin (LOV) is a hypocholesterolemic statin that acts by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which is the rate-limiting enzyme of the mevalonate pathway (Miida et al., 2004). LOV induced apoptosis-like cell death in a Mucor racemosus isolate at relatively high concentrations (Rose and Linz, 1998). Lorenz and Parks, (1990) found that the drug lovastatin (mevinolin) was very effective in lowering the sterol levels of the wild-type yeast Saccharomyces cerevisiae. The natural statins (e.g. SIM and LOV) mainly effect their antifungal activity in their active metabolite forms (hydrolysis of the lactone ring at pH 10), and they proved to be less effective as pro-drugs (Nyilasi et al., 2010). Generally, the synthetic statins are more effective than the natural ones (Galgóczy et al., 2010).

The Azoles

Inhibition of fungal growth by azoles was first described in the 1940s and the fungicidal properties of N-substituted imidazoles were described in the 1960s. Since then, several azoles have been developed to treat various forms of mycosis (Kavanagh, 2011). The azole and triazole antifungal drugs comprise the largest and most widely used class of compounds (Sosa et al., 2010). The azoles also affect fungal sterols but target the biosynthesis of ergosterol rather than the end product itself. The azoles specifically inhibit the cytochrome P450 enzyme CYP51, which catalyzes the 14-demethylation of lanosterol, an essential step in the production of sterols (Georgopapadakou and Walsh, 1999; Edwards et al., 2013), resulting in interruption of membrane synthesis as well as a depletion of ergosterol which then leads to an increase in toxic methylated sterol precursors in the cell membrane. The action of most azoles is considered fungistatic; however, recent studies have indicated a fungicidal activity of micronazole specifically due to accumulation of drug-induced reactive oxygen species within the fungal organism that results in oxidative damage and cell death (CLSI, 2004). Reports suggest that the primary target of azoles is the heme protein, which co-catalyzes cytochrome P-450-dependent 14a-demethylation of lanosterol (Hitchcock et al., 1990). Inhibition of 14a-demethylase leads to depletion of ergosterol and accumulation of sterol precursors, including 14α-methylated sterols (lanosterol, 4, 14-dimethylzymosterol, and 24-methylenedihydrolanosterol), resulting in the formation of a plasma membrane with altered structure and function (Hitchcock et al., 1990). Inhibition of ergosterol biosynthesis has been demonstrated with miconazole, terconazole, ketoconazole, and itraconazole in C. albicans, C. glabrata, C. lusitaniae, P. ovale, T. mentagrophytes, P. brasiliensis, H. capsulatum and A. fumigatus (Vanden and Marichal, 1990).
There are two classes of azoles, the imidazoles which contain two nitrogen atoms in the azole ring and include mainly the topical agents e.g. clotrimazole, miconazole, and ketoconazole. The other groups are the triazoles with three nitrogen atoms in the azole ring and include fluconazole, itraconazole, voriconazole, and posaconazole. The newer azoles like voriconazole and posaconazole have been developed to overcome the limited efficacy of fluconazole against *Aspergillus* spp. and other molds and to improve the absorption, tolerability, and drug interaction profile of itraconazole (Kartsonis et al., 2004). Among species the systemic triazoles vary in their 14 α-demethylase inhibition, which may in part explain the differences in antifungal activity in this class. Asides ergosterol biosynthesis pathway, triazoles have other secondary targets. Depending on the genus, the affinity for these secondary targets varies among the agents. For example, in fluconazole-susceptible *C. albicans*, fluconazole only partially inhibits ergosterol and completely blocks obtusifoliol synthesis, whereas voriconazole completely inhibits both ergosterol and obtusifoliol synthesis (Sanati et al., 1997).

**Imidazoles**

The imidazoles acts by selectively inhibiting the fungal cytochrome P450 that brings about sterol C-14α-demethylation, resulting in decreased ergosterol synthesis and disruption of membrane synthesis in the fungal cell (Stevens et al., 2000). Clotrimazole causes changes in the fungal cell membrane that result in the leakage of intracellular compounds outside of the susceptible cell; clotrimazole may also act to interfere with amino acid transport into fungus (Pfaller et al., 2004). Clotrimazole demonstrates fungistatic activity at concentrations of drug up to 20 mg/ml and may be fungicidal in vitro against *C. albicans* and other species of the genus *Candida* at higher concentrations; it is active in vitro against the dermatophytes *Trichophyton mentagrophytes*, *T. rubrum*, *Epidermophyton floccosum* and *Microsporum canis* (Voss and Pauw, 1999). Ketoconazole exhibited activity against *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*, *Candida* spp. *Malassezia furfur* as well as some dimorphic fungi and dematiaceous agents responsible for chromoblastomycosis (Pfaller et al., 2004). However, it is highly toxic to mammalian cells and relapse is common even after seemingly successful treatment.

**Triazoles**

The triazoles and the imidazoles share the same mechanism of action with both classes selectively inhibiting the fungal cytochrome P450 that causing sterol C-14α-demethylation, and subsequent reduction in ergosterol synthesis and alteration of membrane synthesis in the fungal cell (Stevens et al., 2000). Triazoles, however, have less effect on human sterol synthesis and are metabolized more slowly than imidazoles (Stevens et al., 2000, Bennett, 2005). Fluconazole’s range of activity includes *C. albicans*, most strains of *C. tropicalis*, and *C. parapsilosis*, while most strains of *C. glabrata* demonstrate reduced susceptibility. *C. neoforms*, *Rhodotorula* spp. and *Saccharomyces* spp. are often susceptible (Pappas et al., 2009). Fluconazole exhibits greater activity against yeasts than molds with most *Candida* sp. (except *C. krusei* and *C. glabrata*) and *Cryptococcus neoforms* being susceptible. Itraconazole, another triazole shows wide range of activity against fungal species like *Candida albicans* and some other *Candida* sp, active against *Aspergillus* sp., *C. neoforms*, the dimorphic systemic fungi including *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, the dermatophytes (*Microsporum*, *Trichophyton*, *Epidermophyton*), and many of the dematiaceous moulds (Pfaller et al., 2009). Unlike fluconazole, Itraconazole is often considered to be a mould rather than a yeast agent.

Posaconazole is a lipophilic triazole with structure similar to that of itraconazole. Among the azoles, posaconazole has a significant role in treatment of Zygomycotic infections. Posaconazole has a broad spectrum of activity against yeasts, filamentous, and dimorphic fungi. This includes *Candida* sp., *Cryptococcus neoforms*, *Aspergillus* sp., *Rhizopus* sp., *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides immitis*, dermatophytes, and dematiaceous fungi.

Voriconazole inhibits 24-methylene dihydro-lanosterol demethylase to give increased activity against moulds. The spectrum of activity of voricnazole, a triazole approved in 2005 includes *Candida* spp., including fluconazole-resistant *C. krusei* and *C. glabrata* (Pfaller et al., 2006). Other susceptible yeasts include *Cryptococcus neoforms* and *Trichosporon beigelli* and *Saccharomyces cerevisiae* (Pfaller et al., 2006). Its range of activity also includes the dimorphic systemic fungi e.g. *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and some strains of *Pseudallescheria boydii* are also susceptible in vitro (Torres-Rodriguez and Alvarado-Ramirez, 2007).

**Allylamines and thiocarbamates**

The allylamines and the thiocarbamates are antimycotics that demonstrates exceptionally high activity against dermatophytes, but have a rather weak effect against
yeasts. They are noncompetitive inhibitors of the enzyme squalene epoxidase, involved in the cyclisation of squalene to lanosterol (Petanyi et al., 1984; Georgopapadakou and Walsh, 1996). Fungal cells affected by these compounds accumulate squalene with a simultaneous decrease of ergosterol content, which alters membrane properties (Polak, 1990). Thiocarbamates and allylamines have a naphthalene moiety in common, which may be involved in binding to the enzyme (Polak 1990). They have shown minimal cross-reactivity with the mammalian enzyme involved in cholesterol synthesis. The morpholine amorolfine, a topical antifungal agent for the treatment of onychomycosis, acts via inhibition of Δ^{14}-reductase and Δ^{7}, Δ^{8}-isomerase, which are also enzymes in ergosterol synthesis (Mercer, 1991; Haria and Bryson, 1995).

Terbinafine is an allylamine that reversibly inhibits squalene epoxidase, an enzyme that acts early in the ergosterol synthesis pathway. This inhibition produces both the fungistatic and fungicidal effects on fungal cells. Terbinafine demonstrates excellent in-vitro fungicidal activity against many dermatophytes including Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis and Epidermophyton floccosum (Darkest et al., 2003). It generally demonstrates fungicidal activity against Candida parapsilosis but it is fungistatic against C. albicans and other Candida spp. The in vitro spectrum of activity also includes Aspergillus spp., some dimorphic fungi and Sporothrix schenckii.

Butenafine is a benzylamine derivative, structurally similar to the allylamines (e.g., terbinafine), except that a butyl benzyl group replaces the allylamine group (White, 1999). Butenafine inhibits the conversion of 2, 3-oxydosqualene, a reaction catalyzed by the enzyme squalene epoxidase, thus it subdues ergosterol biosynthesis by blocking squalene epoxidation. Like the allylamines, the benzylamine derivatives block an earlier step in ergosterol biosynthesis than do the azoles. Butenafine is a fungicidal antymycotic, with activity against the dermatophytes including Epidermophyton floccosum, Trichophyton mentagrophytes, T. rubrum, and T. tonsurans (Syed and Maibach, 2000).

Naftidif is an allylamine that suppresses the biosynthesis of ergosterol at an earlier stage of the metabolic pathway than the azoles, independent of cytochrome P450 enzymes, by inhibiting the activity of squalene epoxidase. The resulting ergosterol deficiency is accompanied by an accumulation of squalene in the fungal cell that leads to cell death (Maeda et al., 1991). Naftidif is a fungicidal compound with activity mainly against dermatophytes such as Trichophyton rubrum, Trichophyton mentagrophytes, T. tonsurans, and Epidermophyton floccosum, and Microsporum canis, M. audouinii, and M. gypseum. Fungistatic activity has been shown in vitro against C. albicans.

**Morpholines**

The morpholines are synthetic antifungals that inhibit the reductase and isomerase enzymes in ergosterol biosynthesis. Morpholines are analogues of the high energy carbo-cationic intermediates formed by these enzymes (Polak, 1990). Their antifungal activity is mainly due to the inhibition of the reductase, since it, unlike the isomerase, is an essential enzyme (Georgopapadakou and Walsh, 1996). The accumulation of dimethyl-lanosterol and depletion of ergosterol alters the composition of fungal cell membranes. Dermatophytes are among the fungi most sensitive to amorolfine, while yeasts are only moderately sensitive. Molds vary in sensitivity, with Aspergillus spp. being resistant and Alternaria spp. being highly sensitive (Polak, 1990).

**Amino acids and peptides**

Single amino acids as well as peptides and proteins have been found to have antifungal activities. A large group of cyclic peptides, lipopeptides and lipodepsipeptides (containing one or several ester bonds) have been isolated on their antifungal activity, and they act by several different modes of action (Ziegelbauer et al., 1998).

**Cyclic peptides**

Of the antifungal cyclic peptides, aureobasidin has gained much attention since its discovery (Ikai et al., 1991). Aureobasidins are a group of cyclic depsipeptides with antifungal activity produced by Aureobasidium pullulans (Yoshikawa et al., 1993). Aureobasidins are composed of eight amino acids and one hydroxy acid such as 2-hydroxy-3-methylpentanoic acid (Hmp), and highly lipophilic and showed inhibitory activity against the enzyme inositol phosphoceramide (IPC) synthase, critical in fungal sphingolipid biosynthesis. Sphingolipids, in turn, are vital for the function of the cell membrane for fungi and humans alike. The IPC enzyme, on the other hand, is lacking in mammals, which means that all compounds selectively inhibiting IPC are highly interesting for development of antifungal drugs. The inhibition of this enzyme results in the depletion of essential sphingolipids in the fungal cells. Since all fungi have this enzyme, Aureobasidin A is potentially a broad spectrum antifungal (Takesako et al., 1991; 1993). Three of the new aureobasidins, S2b, S3 and S4, which have hydroxylated Hmp as the hydroxy acid, were highly active against Candida spp. and Cryptococcus neoformans.
Lipopeptides

Lipopeptides from Bacillus species, includes the surfactins, iturins, and fengycins. The surfactins are powerful surface-active compounds, which show antibacterial activity but no marked fungitoxicity (Ongena and Jacques, 2008). Iturins are a crucial family of these cyclic lipopeptides and they are derived only from B. subtilis and B. amyloliquefaciens and exhibit strong antifungal activities against a wide variety of yeasts and plant pathogenic fungi (Zhang et al., 2013). It has been proposed that antimicrobial activity of iturins depends predominantly on its capacity to increase membrane permeabilization, which is being attributed to aggregates formed by iturin molecules, iturin–phospholipid complex or iturin–phospholipid–sterol complex (Maget-Dana and Peypoux, 1994). Microscopic observations (SEM and TEM) revealed that growth inhibition of Rhizopus solani as a response to Bacillomycin L was accompanied by marked morphological and cytological changes, including rough cell surface, condensation of the cytoplasmics and irregular architecture of organelles (Zhang et al., 2013). Fengycins are the main lipopeptides having strong antifungal activities (Ongena and Jacques, 2008). It has antifungal activity against filamentous fungi. It inhibits filamentous fungi but is ineffective against yeasts (Deleu et al., 2008).

Lipodepsinonapeptides

Many strains of Pseudomonas syringae pv. syringae produce one of four classes of small cyclic lipodepsinonapeptides: syringomycins (Segre et al., 1989), syringotoxins (Ballio et al., 1990; Harrison et al., 1991) syringostatins (Isogai et al., 1990), and pseudomycins (Ballio et al., 1994). These metabolites are phytotoxic and growth inhibitory against a wide range of fungi (Sorensen et al., 1994). They are thought to interact with the fungal cell membrane by pore formation, which results in fatal electrolytic leakage (Bender et al., 1999) and have been demonstrated to show activity against Candida spp. and Aspergillus spp. All of them have shown inhibitory activity against yeasts such as Rhodotorula pilimanae and S. cerevisiae (Takekoto, 1992).

Syringomycins’ mechanism of action involves formation of ion channels in the fungal plasma membrane employing a novel sphingolipid-modulated channel formation mechanism. Takekoto et al. (2002) found out that plasma membrane pore formation is the mechanism of syringomycin E action and that pore formation is modulated by plasma membrane sphingolipids. Earlier, Zhang and Takekoto (1989) found that Syringomycin stimulated potassium efflux by yeast cells by stimulation of one or more protein kinases of the host plasma membrane. Also, plasma membrane-associated mannosyl-inositolphospho-ceramides (sphingolipids) were shown to promote growth inhibition ability of syringomycin E in yeast (Bessonov et al., 2006). It is speculated that these surface lipids participate in membrane pore forming mechanisms involving physical interactions with syringomycin E (Bessonov et al., 2006). Syringomycin E-glycolipid mixtures display fungicidal activities that are 2 to 5-fold more potent than with syringomycin E alone (Kaulin et al., 2005). Pseudomycin A is the predominant peptide in a family of four including syringomycin, syringotoxin and syringostatins, and has showed selective phytotoxicity, as well as having impressive activity against Candida albicans. Previous studies have shown that pseudomycins are different from previously described antimycotics from P. syringae (Segre et al., 1989; Bidwai et al., 1986; Ballio et al., 1988; Gross et al., 1977; Isogai et al., 1989). Pseudomycin A contains hydroxyaspartic acid, aspartic acid, serine, arginine, lysine and diaminobutyric acid and alongside other Cyclic lipodepsinonapeptides (CLPs), target the fungal plasma membrane by altering several membrane functions such as membrane potential, protein phosphorylation, H1-ATPase activity, and cation transport fluxes (Sorensen et al., 1996).

CONCLUSION

The ability to selectively target fungal cell components instead of mammalian components given similarities is the ultimate goal in the development of antifungal agents. Various components of fungi cell membrane are targets for the polyenes, azoles, allylamines, lipopeptides and statins and they have shown remarkable activity against mycotic infections. Ergosterol, a sterol unique to fungal cell has been exploited in the development of antifungals and is the major target of polyenes and azoles, while others target specific enzymes important in membrane functions. However, some of these agents though potent, cross react with human cellular components e.g. sterols hence resulting in toxicity to the host. This has limited the use of antifungals to topical applications mostly. It is suggested that in the further development of antifungal agents, it should aim at synthesizing less toxic compounds with corresponding high antifungal activity and reduced possibility of resistance.

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REFERENCES


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