

Research Article

Antimycolytic agents: fungistatic and fungicide

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Abstract

Invasive fungal infections are described as a continuous and severe harm to human health and they are associated with at least 1.5 million deaths worldwide each year. Amphotericin B exerts its activity through hydrophobic interactions with cell membrane ergosterol, cause the rupturing or leakage of cell membrane. The antifungal azole medicine group is classified as imidazoles (clotrimazole, ketoconazole, miconazole) and triazoles (fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole) that are named according to the number of nitrogen atoms in the azole ring. Flucytosine is a first-line treatment for the management of cryptococcal meningitis. The most routine adverse effects of fluconazole involve accelerated liver enzymes, gastrointestinal complaints, headache, and skin rash. If antacids, PPIs, H2 blockers administered together with ketoconazole medicines; they will reduce the blood levels of ketoconazole by increasing gastric pH because ketoconazole requires an acidic media for dissolution and systematic absorption. Griseofulvin ruptures mitotic spindle during metaphase by interacting with fungal microtubules(-), fungal mitosis (metaphase arrest), adequate to block expansion of fungi (drug is static), preventing them from damaging.

Introduction

Fungal infections are caused by microscopic organisms that can damage the epithelial tissue. The fungal kingdom involves yeasts, molds, rusts and mushrooms [1]. Fungi, like animals, are hetrotrophic, that is, they obtain nutrients from the ambient, not from endogenous origins (like plants with photosynthesis). Most fungi are advantageous and are included in biodegradation, nevertheless, a few can cause opportunistic infections if they are interpolated into the skin via wounds, or into the lungs and nasal route if inhaled [2]. Diseases caused by fungi include superficial infections of the skin by dermatophytes in the microsporum, trichophyton or epidermophyton genera. These dermophytic infections are named for the site of infection rather than the causative organism [3,4]. Invasive fungal infections are described as a continuous and severe harm to human health and they are associated with at least 1.5 million deaths worldwide each year [5,6]. Fungal infections are routine in immunocompromised patients, as displayed in their chemotherapy, acquired immune deficiency syndrome, and/or organ transplantation [7]. The infection caused by fungi of the genus paracoccidioides was first defined by Adolpho Lutz in 1908. In 1971, during the meeting of many mycologists from Latin America in Medellín-Colombia, the term Paracoccidioidomycosis was made to require the systemic granulomatous infection caused by the thermodimorphic fungi of the genus paracoccidioides [8,9].

More Information

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Keywords: Antimycolytic; Fungistatic; Fungicide

Abbreviations: ADRS Adverse Drug Reactions; ATP: Adenine Triphosphate; CYP450: Cytochrome P450; DNA: Deoxyribonucleic; DI: Drug Interaction; 5FU: 5-Fluorouracil; PCM: Paracoccidioidomycosis; PH: Potenz Hydrogen; P-gp: Pglycoprotein; RNA: Ribonucleic Acid; SJS: Stevens Johnson Syndrome



Antimycolytic agents

Recently, four antifungal classes of medication named as azoles (imidazoles such as ketoconazole, clotrimazole, miconazole, tioconazole, econazole and triazoles such as fluconazole, vorioconazole, itraconazole, posaconazole), polyenes (amphotericin B and nystatin), pyrimidines (flucytosine) and echinocandins (caspofungin, micafungin and anidulafungin) are mostly used by clinicians and veterinarians for systemic treatment. Antifungals have various drawbacks in terms of toxicity, spectrum of activity, safety and pharmacokinetic properties [10,11] (Figure 1).

Antifungal antibiotics (polyenes): i. Amphotericin B; ii. Nystatin.

Amphotericin B

Amphotericin-B is polyene antibiotic and it is produced by bacterial strain of streptomyces nodusus using fermentation with antifungal activity. Amphotericin-B is an amphipathic polyene antibiotic which permeabilizes ergosterol-containing membranes [12] (Figure 2).

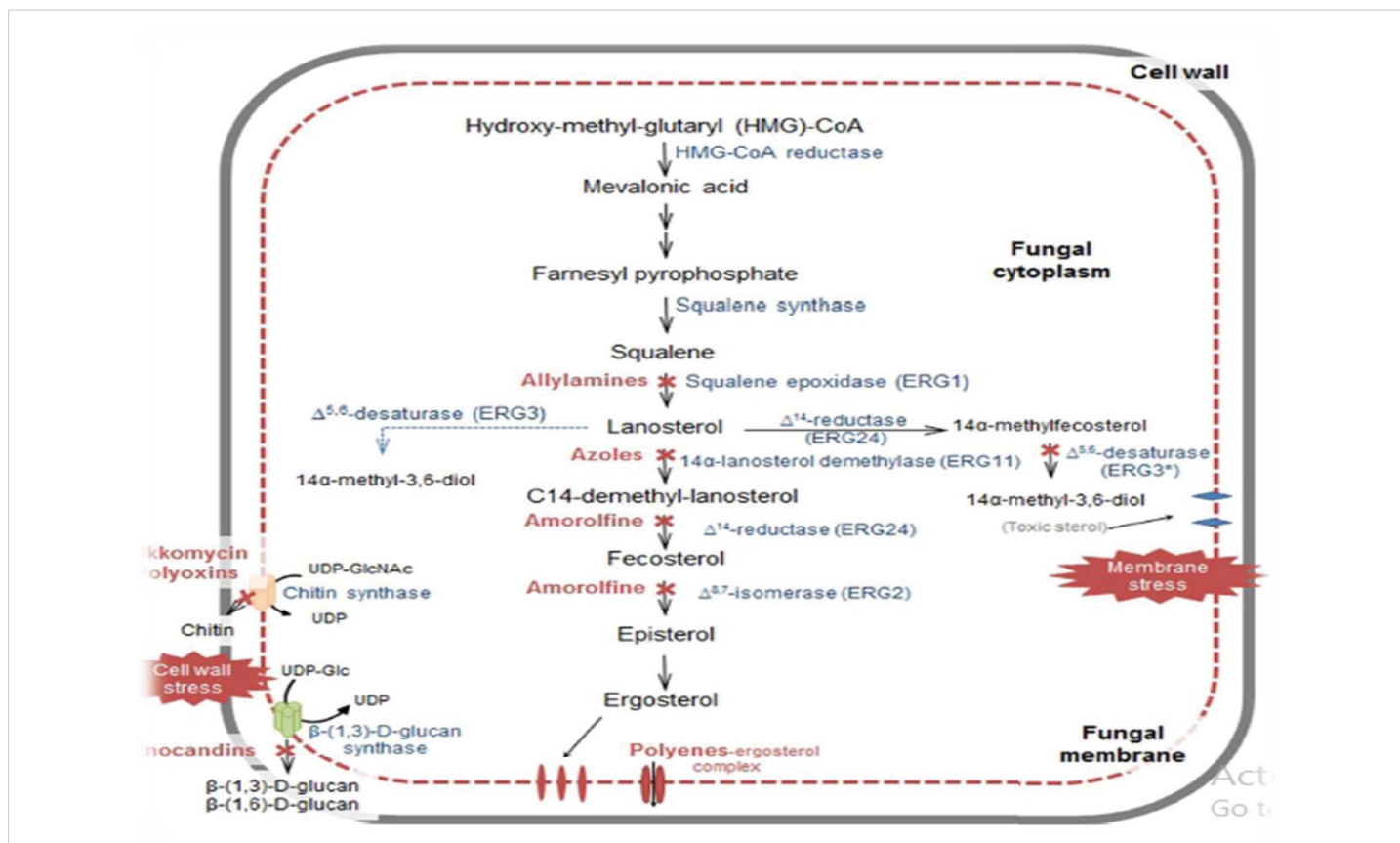


Figure 1: schematic illustration of antifungal agents' site of actions.

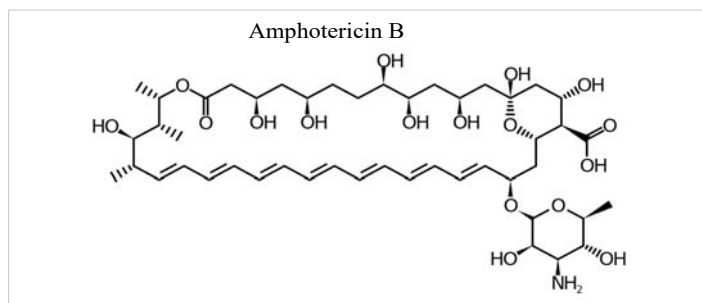


Figure 2: Chemical structure of Amphotericin B.

Mechanism of action: Amphotericin-B binds to the sterols in fungal cell membrane and generates transmembrane channel and electrolyte leakage. Amphotericin B exerts its activity through hydrophobic interactions with cell membrane ergosterol, cause the rupturing or leakage of cell membrane and pores formation permits the efflux of potassium, eventually leading to cell death [13].

Spectrum of activity: Amphotericin B has high activity against *Cryptococcus* spp and most *Candida* spp, *Candida albicans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Aspergillus*, *Rhodotorula* with the exception of *Candida lusitanae*, which commonly is found to have greater minimal inhibitory concentrations [14,15].

Clinical use: Amphotericin B was the first antifungal medicine developed and is confirmed for the treatment of multiple invasive fungal infections involving candidiasis,

aspergillosis, cryptococcosis, blastomycosis, histoplasmosis, mucormycosis, and sporotrichosis. Amphotericin B injection is used for treatment of severe and potentially life-threatening fungal infections [16,17].

Adverse drug effects: Intravenous amphotericin is toxic, causing fever, chills, hypotension during infusion, nephrotoxicity, electrolyte abnormalities and transient bone marrow suppression. Kidney damage is the most severe adverse effect of amphotericin B. Systemic toxicity (particularly nephrotoxicity) of amphotericin is lowered by using the liposomal/ lipid/micellar formulations. Certain side effects of Amphotericin B are anaphylactic reaction, leukoencephalopathy, cardiac arrhythmias, convulsions, and cardiorespiratory collapse [18].

Contraindications: Amphotericin B is not given for patients who have documented history of hypersensitivity; for nursing mother and individuals who take anticancer medications [19].

Drug interaction: If amphotericin-B is combined with 5-flucytosine; they have synergistic effect and used in severe infections and immunosuppressed patients [20,21]. Concomitant administration of vancomycin and aminoglycoside (both increase risk of nephrotoxicity) with amphotericin-B increases the risk of renal impairment and electrolyte disturbances. Coadministration of amphotericin B with immunosuppressants, such as tacrolimus or

cyclosporine, in transplant recipients may be increases the risk of bone marrow suppression or amphotericin B accelerates myelosuppressive toxicity of antineoplastic medication. If ketoconazole and amphotericin-B are administered concurrently they have antagonistic/contraindicated effects [22,23].

Antimetabolite/fluorinated pyrimidine: Flucytosine

Flucytosine is antimetabolite that enters fungal cells via cytosine permease where it is converted to fluorouracil, which acts as false nucleoside inhibiting synthesis of both DNA and RNA [24] (Figure 3).

Mechanism of action: 5-Fluorouracil impairs synthesis of nucleic acid, eventually interfering with protein synthesis as well and also blocks thymidylate synthetase and thus DNA synthesis mammalian cells remain unaffected except few bone marrow cells. The drug enters the fungal cell via active transport on ATPases that normally transport pyrimidines. Once inside cells, fungal cytosine deaminase change the medicine to active 5FU, a very effective antitumor agent, which is integrated into RNA causing faulty RNA synthesis and also is a tough, non-competitive inhibitor of thymidylate synthesis interrupting the one carbon pool substrate. Mammalian cells do not contain cytosine deaminase [24-29] (Figure 4).

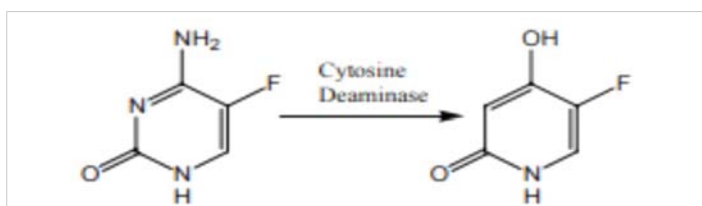


Figure 3: Chemical structure of Flucytosine.

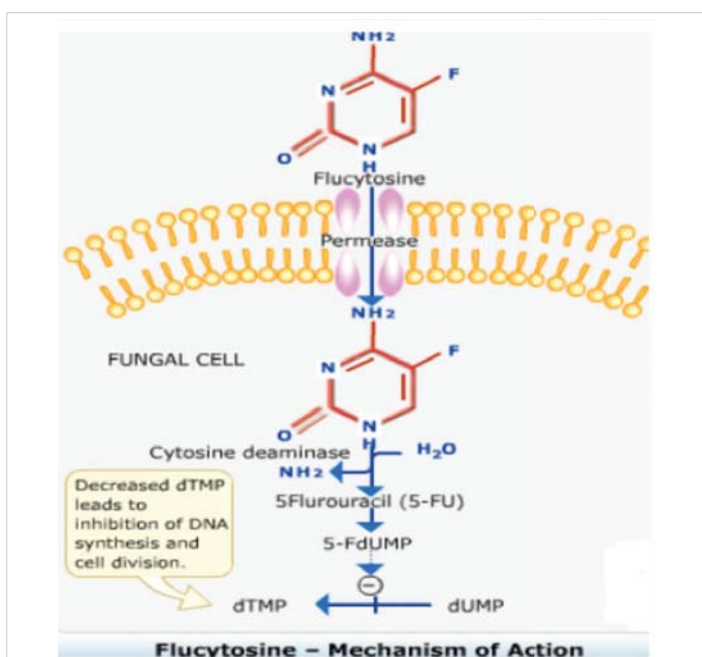


Figure 4: Mechanism of action of Flucytosine.

Spectrum of activity: Flucytosine is act on routine pathogenic treatment. Its spectrum of activity involves multiple candida spp, involving *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*. *C. krusei* and *C. lusitaniae* are also involved in the spectrum but MICs are greater [30,31].

Clinical use: Flucytosine is a first-line treatment for management of cryptococcal meningitis and administered with amphotericin B during the induction period. Whereas, flucytosine has high activity against most candida spp, resistance elaborates hastily during use, limiting its treatment potential as a single agent [32,33].

Adverse drug effects: Flucytosine cause mild BM depression; loss of hair; and dose should be decreased in the presence of renal impairment [34].

Contraindications: Flucytosine is not indicated for individuals who are hypersensitive to the drugs and its derivatives [35].

Drug interaction: Concomitant administration of flucytosine with NSAIDs such as naproxen or ibuprofen may be increases the risk of kidney problems. Concurrent administration of flucytosine with cotrimoxazole, cancer chemotherapy and etc they aggravate bone marrow suppression [36,37].

Azoles (imidazoles and triazoles)

The azole antifungal drug is classified as imidazoles (clotrimazole, ketoconazole, miconazole) and triazoles (fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole) that are named corresponding to the number of nitrogen atoms in the azole ring [3,38].

Mechanism of action: Azoles exert their action by inhibiting the fungal cytochrome P450 3A enzyme (lanosine 14 α -demethylase) demethylation of lanosterol in fungi, which interferes with the synthesis of ergosterol in the fungal cell membrane [41].

Ketoconazole

Ketoconazole is a broad spectrum antifungal agent that belongs to biopharmaceuticals classification system (BCS) class II drug means ketoconazole has low solubility and high permeability which exhibits dissolution rate-limited absorption [40] (Figure 5).

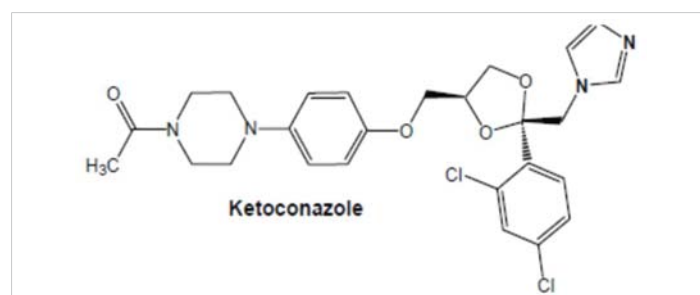


Figure 5: Chemical structure of Ketoconazole.

Mechanism of action: Ketoconazole is act by inhibiting the synthesis of ergosterol, the fungal equivalent of cholesterol, thereby elevating membrane fluidity and suppressing growth of the fungus [41] (Figure 6).

Spectrum of activity: Ketoconazole is rarely used at present for treatment or prophylaxis of fungal infections. Ketoconazole is used for treatment of infections caused by a fungus and yeast [42,43].

Adverse drug reactions: Ketoconazole cause nausea and vomiting, worse with greater doses (800 mg/day) and also cause hepatotoxicity, accelerate in transaminases, hepatitis, anti-androgenic effects decreasing of CYP P450 responsible for testosterone synthesis (dose related). Gynecomastia, oligosperma, decreased libido dose-related blockage of CYP P450 responsible for adrenal cortisol synthesis is ketoconazole mild side effects [44,45].

Contraindications: Ketoconazole is not indicated for individuals who have previously liver disease; porphyria; hypersensitivity to the drugs and its derivatives [46].

Drug interaction: If antacids, PPIs, H2 blockers administered together with ketoconazole medicines; they will reduce the blood levels of ketoconazole by increasing gastric pH because ketoconazole requires an acidic media for dissolution and systematic absorption. If ketoconazole administered with potent inhibitor of cytochrome P450 3A4 such as rifampin and phenytoin; they decrease ketoconazole blood levels. If ketoconazole administered with cyclosporin, warfarin, and astemizole, corticosteroid, and theophylline; it increases their blood levels. If ketoconazole is given together with an inhibitor of multiple CYP isozymes and P-gp; it can importantly accelerate serum concentrations of multiple medicines [47-49].

Fluconazole

The pharmacokinetic characteristics of the individualazole medicines are different due to their variation in molecular weight, solubility, and protein binding. Fluconazole is idiomatic due to its low molecular weight and great aqueous solubility. It establishes great bioavailability, approximately 90%, and its absorption is not affected by gastric acidity or food [50-53] (Figure 7).

Spectrum of activity: Fluconazole is active against

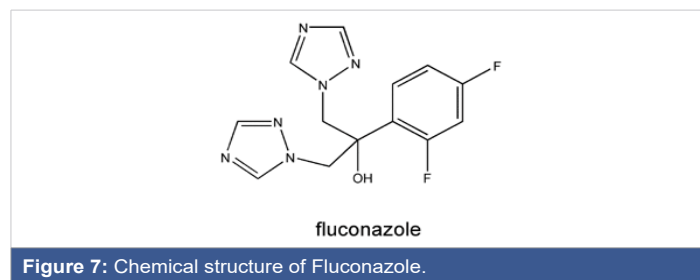
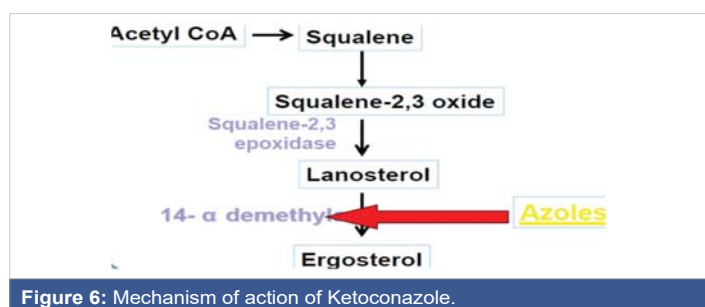


Figure 7: Chemical structure of Fluconazole.

multiple medically significant candida spp, involving *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. lusitaniae*, and *C. dubliniensis*. It has reasonable activity against coccidioides spp. and *cryptococcus neoformans* and certain activity against *Histoplasma capsulatum*. The medication has no clinically important activity against most molds, involving aspergillus spp., fusarium spp., and the mucorales (previously called Zygomycetes), such as mucor spp. and rhizopus spp [54-56].

Clinical use: Fluconazole is indicated for treatment of both mucosal and systemic candidiasis, the treatment of cryptococcosis, and prophylaxis for candidiasis [57].

Adverse drug reactions: The most routine adverse effects of fluconazole involve accelerated liver enzymes, gastrointestinal complaints, hepatotoxicity, headache, and skin rash involving SJS. Fluconazole is used cautiously in patients with renal impairment [58,59].

Contraindications: Fluconazole is not given for individuals who are hypersensitive to the medicine and its derivatives [60].

Drug interactions: Fluconazole administration perhaps accelerates the consequences of oral hypoglycemic and decreases the metabolism of phenytoin and warfarin. Concomitant use of fluconazole with other medicines known to extend the QT interval, especially those metabolized by CYP2C9, 2C19 or 3A4, perhaps increase the risk of QT prolongation and torsades de pointes. Taking fluconazole with the potent CYP enzyme inducer such as warfarin, theophylline, rifampin etc can decrease fluconazole serum concentrations, possibly to subtherapeutic levels [61,62].

Itraconazole

Absorption of the itraconazole capsule formulation is comparatively 55% but it is improved with gastric acidity and food intake. Therefore, it is recommended to be administered with an acidic beverage and food [63-65] (Figure 8).

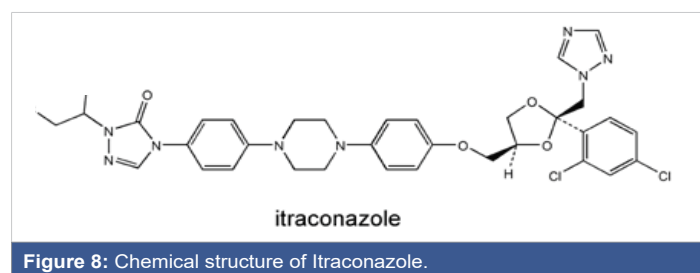


Figure 8: Chemical structure of Itraconazole.

Spectrum of activity: Like fluconazole, itraconazole substantiates activity against most candida spp, with greater MICs for *C. glabrata* and *C. krusei*/Itraconazole has a wider spectrum of activity than fluconazole and also active against a broad spectrum of fungi involving *C. neoformans*, aspergillus spp., *alastomyces dermatitidis*, coccidioides spp., *h. capsulatum*, *paracoccidioides brasiliensis*, sporothrix spp., and dermatophytes. It is also active against most species of candida. Itraconazole has no clinically important activity against fusarium spp. or the mucorales and has variable activity against scedosporium spp [66,67].

Clinical use: Itraconazole is confirmed for the treatment of many mycoses, involving blastomycosis, mucosal candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, onychomycosis, and sporotrichosis [68-70].

Adverse drug reactions: The most routine adverse effects of oral itraconazole are nausea, diarrhea, vomiting, pulmonary oedema, menstrual disorders, heart impairment, dyspepsia, abdominal pain, hypokalemia, elevated liver enzyme values, anaphylaxis, liver injury, and rash involving SJS and severe hepatic toxicity [71,72].

Drug interactions: Absorption of the itraconazole oral capsules and the posaconazole oral solution is optimized by gastric acidity, so proton pump inhibitors and histamine-2 blockers should be avoided because they minimize gastric acidity of the stomach which is required for the absorption of itraconazole oral capsules and the posaconazole oral solution derivatives. Taking itraconazole with a CYP3A4 substrate that extends the QT interval increases the risk of QT prolongation and torsades de pointes. Itraconazole is also a P-gp inhibitor and can accelerate serum concentrations of P-gp substrates [73-75].

Voriconazole

Absorption is not affected by gastric acidity and is optimal in the fasted state. Loading doses for the first 24 hours are recommended to more rapidly achieve therapeutic levels [76,77] (Figure 9).

Spectrum of activity: Voriconazole has a spectrum of activity identical to that of itraconazole, but is clinically measured to be more active against aspergillus spp. and most species of candida, involving *C. glabrata* and *C. krusei*.

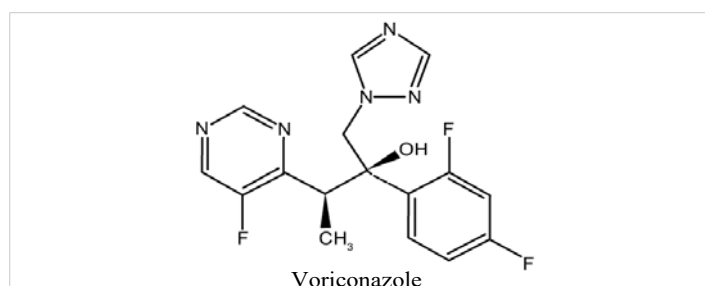


Figure 9: Chemical structure of Voriconazole.

Voriconazole is active against fusarium spp. and scedosporium spp, but it is not active against the mucorales; infection with these organisms has advanced during treatment with voriconazole [78,79].

Clinical use: Voriconazole is confirmed for the treatment of invasive aspergillosis, esophageal candidiasis, invasive candidiasis, scedosporiosis, and fusariosis [80].

Adverse drug reactions: In general, the triazole medicines are fairly well-tolerated. Side-effects include rash, headache, or gastrointestinal upset. Hepatotoxicity marked by acceleration of liver chemistry tests and, least routinely, liver failure, is the most routine and severe group of side effect. Long-term administration of voriconazole perhaps cause painful periostitis of long bones, premature aging, and an elevated occurrence of squamous cell carcinoma or melanoma in sun-exposed skin transient visual disturbances involving blurred vision, photophobia and changed perception of color or image have happened in about 20% of patients treated with voriconazole [81].

Contraindications: Voriconazole is not indicated for breastfeeding mother; for individuals who are hypersensitive to drugs and its derivatives [82].

Drug interactions: The triazoles can cause QT prolongation due to drug-drug interactions perhaps happened by the additive effect of additional QT prolonging agents [83,84]. Voriconazole is a substrate of CYP2C19, 2C9 and 3A4. Medicines that block or induces alone or most of these pathways perhaps importantly alter serum concentrations of voriconazole. Concomitant use of voriconazole with other medicines that extend the QT interval, particularly those metabolized by CYP2C9, 2C19 or 3A4, perhaps increase the risk of QT prolongation and torsades de pointes [85].

Allylamine e.g. Terbinafine

Terbinafine is a synthetic allylamine antifungal. Terbinafine is a highly lipophilic base and consequently has very high volume of distribution a strong and non-specific binding to plasma proteins [86] (Figure 10).

Mechanism of action: Terbinafine acts by interfering with ergosterol biosynthesis by blocks the fungal enzyme squalene epoxidase. This leads to the concentration of the sterol squalene, which is toxic to the organism [87] (Figure 11).

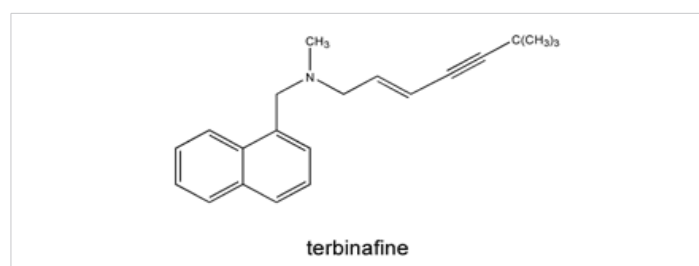


Figure 10: Chemical structure of Terbinafine.

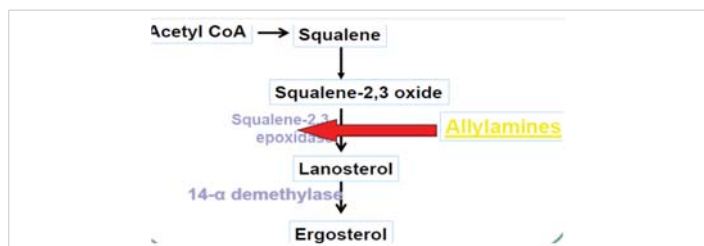


Figure 11: Mechanism of action of Terbinafine.

Use: Terbinafine is used for treatment of superficial mycoses (fingernail, toenail); systematic mycoses [88].

Adverse drug reaction: Orally administered terbinafine may cause nausea, vomiting, changed taste, headache, and tiredness. Topical application of terbinafine perhaps causes burning, stinging, redness, itchiness, and drying of the skin [89].

Contraindications: Terbinafine is not given for breastfeeding mother; individuals who have active or severe liver disease; those who are hypersensitive to the medications and its derivatives.

Drug interaction: Coincident administration of fluconazole and terbinafine perhaps accelerates the serum concentrations of terbinafine. Cimetidine perhaps decreases the clearance of terbinafine if administered together, and enzyme inducers drugs such as rifampin perhaps increase terbinafine clearance if administered concomitantly [90].

Other antibiotics (Griseofulvin)

Griseofulvin is antibiotic produced by the mycelial fungus *penicillium patulum*. It is a mycotoxic metabolic product of *penicillium* spp [91] (Figure 12).

Mechanism of action: Griseofulvin ruptures the mitotic spindle during metaphase by interacting with fungal microtubules(-), fungal mitosis (metaphase arrest), which is adequate to block growth of fungi (medicine is static), eventually damaging fungi cell membrane [91].

Spectrum of activity: Griseofulvin are used for the treatment of systemic antifungal to manage topical ringworm infections, e.g., onychomycosis, tinea capitis, tinea pedis, etc [92].

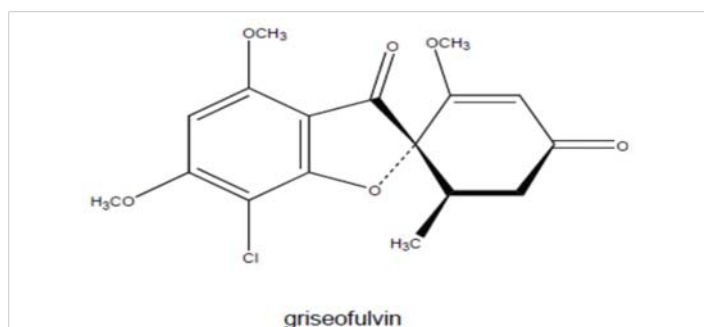


Figure 12: Chemical structure of Griseofulvin.

Use: Griseofulvin is indicated for treatment *tinea capitis*; *tinea unguium*; pedis caused by fungi and griseofulvin used for treatment of skin infections such as athletes foot, jock itch etc.

Adverse drug reactions: Griseofulvin cause GI disturbances, allergic reactions, skin rash, headache, photosensitivity, angioedema, peripheral neuritis, lethargy, mental confusion, blurring of vision, vertigo, being an antimiototic (bone marrow suppression), leucopenia, neutopenia [93].

Contraindications: Griseofulvin is not given for patients who have porphyria; severe liver disease.

Drug interactions: If griseofulvin administered with OADs and OCs, it antagonizes their effects. Concurrent administration of griseofulvin with AEDs such as phenobarbital, is decreases the gastrointestinal absorption of AEDs. Concomitant administration of griseofulvin with CYP450 enzyme inducers medications such as hypnotic's perhaps decreases plasma concentrations of griseofulvin. If griseofulvin given with alcohol, it causes disulfiram like reaction [94].

Conclusion

Fungi, like animals, are hetrotrophic, that is, they obtain nutrients from the ambient, not from endogenous origins (like plants with photosynthesis). Amphotericin B was the first antifungal drug developed and is confirmed for the treatment of multiple invasive fungal infections enclosing candidiasis, aspergillosis, cryptococcosis, blastomycosis, histoplasmosis, mucormycosis, and sporotrichosis. Intravenous amphotericin is toxic, causing fever, chills, hypotension during infusion, nephrotoxicity, electrolyte abnormalities and transient bone marrow suppression. The absorption of itraconazole is decreased by medicines that accelerate gastric pH, such as antacids, H₂-receptor blockers and proton pump inhibitors. Orally administered terbinafine perhaps cause nausea, vomiting, altered taste, headache, and tiredness. Topical application of terbinafine perhaps causes burning, stinging, redness, itchiness, and drying of the skin.

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Data sources: Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, and Cochrane database. Search terms included: antimycolytic agents both fungistatic and fungicide

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