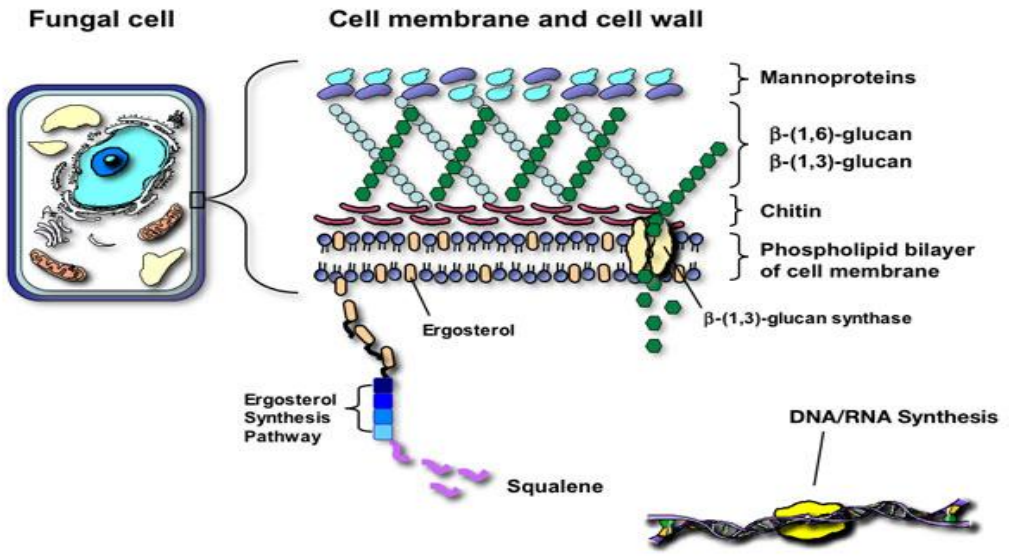
Medical mycology (Le.2) **D.Hamzia Ali**

ANTIFUNGAL AGENT

Knowledge of fungal cell structure and function is essential for understanding the pharmacology of antifungal agents. Like mammalian cells, fungi are eukaryotes with DNA organized into chromosomes within the cell nucleus and have distinct cytoplasmic organelles including endoplasmic reticulum, Golgi apparatus, mitochondria, and storage vacuoles. This homology to mammalian cells also extends to biosynthetic pathways, where fungi share similar mechanisms for DNA replication and protein synthesis.

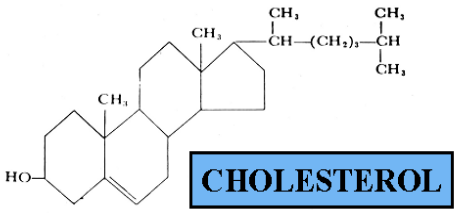
Fungal plasma membranes are similar to mammalian plasma membranes, differing in having the nonpolar sterol ergosterol, rather than cholesterol, as the principal sterol. The plasma membrane regulates the passage of materials into and out of the cell by being selectively permeable. Membrane sterols provide structure, modulation of membrane fluidity, and possibly control of some physiologic events.



1- Polyene Antifungal Drugs

The polyene compounds are so named because of the alternating conjugated double bonds that constitute a part of their macrolide ring structure . The polyene antibiotics are all products of *Streptomyces* species. These drugs interact with sterols in cell membranes (ergosterol in fungal cells; cholesterol in human cells) (Fig. 2). to form

pores that increase permeability to proteins and cations, eventually leading to cell death. The polyene antifungal agents include nystatin, amphotericin B, and pimaricin. Ergosterol is similar to mammalian cholesterol, thus agents binding ergosterol may have a cytotoxic effect in the host tissue. Ergosterol has two conjugated double bonds that are lacking in mammalian sterols.



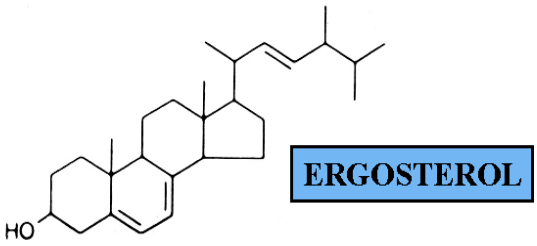


Fig.1: Ergosterol and Cholesterol .

Amphotericin B , Other Names: **(**Fungizone, Amphotericin B Lipid Complex, Liposomal Amphotericin B) is the antifungal agent for treatment of life-threatening mycoses and for most other mycoses, with the possible exception of the dermatophytoses. Discovered by Gold in 1956, . Its broad spectrum of activity includes most of the medically important moulds and yeasts, including dimorphic pathogens such as *Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis, and Paracoccidioides brasiliensis*. It is the drug of choice in treating most opportunistic mycoses caused by fungi such as *Candida* species, *Cryptococcus neoformans, Aspergillus* species, and the Zygomycetes.

Toxicities of polyene antifungals are an extension of their mechanism of action. Stimulation of the host immune cells by amphotericin B causes release of inflammatory cytokines by monocytes resulting in fever, chills, nausea, vomiting, and headache during intravenous infusions. At higher concentrations, amphotericin B binds to cholesterol in mammalian cell membranes leading to various organ toxicities, most importantly nephrotoxicity.

During the 1990s, newer lipid preparations of amphotericin B, There are 2 formulations of amphotericin:

- Deoxycholate (standard)
- Lipid-based

Several **lipid vehicles** reduce the toxicity of amphotericin B (particularly nephrotoxicity and infusion-related symptoms). Two preparations are available:

- Amphotericin B lipid complex
- Liposomal amphotericin B

Lipid formulations are preferred over conventional amphotericin B because they cause fewer infusion-related symptoms and less nephrotoxicity

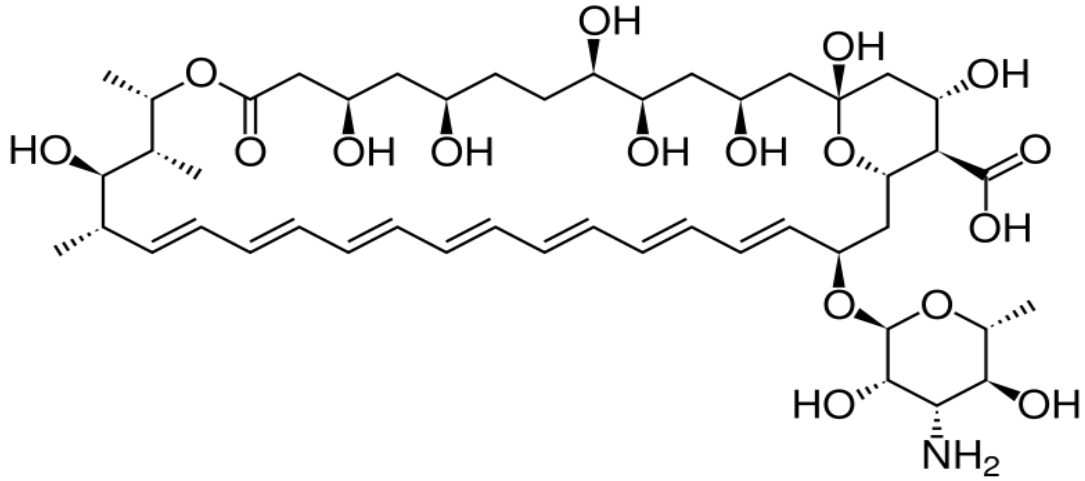
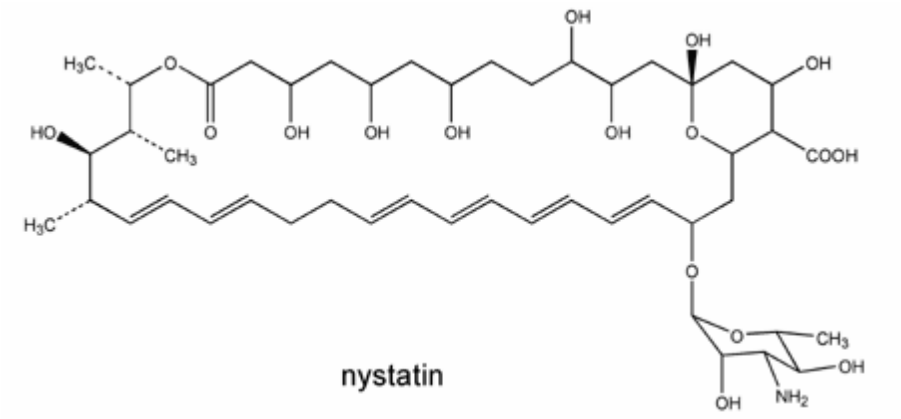


Fig.2: Amphotericin B

Nystatin was the first successful antifungal antibiotic to be developed, and it is still in general use. The promise of its broad-spectrum antifungal activity is offset by host toxicity. Therefore, it is limited to topical use, where it has activity against yeasts such as the Candida species.

Indications: Nystatin was originally isolated from *Streptomyces noursei* in 1951.
Disposition: Available in oral tablets, powder for suspension, vaginal tablets, pastilles, for local therapy only (not absorbed). Nystatin will treat gut candidiasis.
Adverse Effects: No significant adverse effects with these uses, however itching, irritation and burning may occur. Rarely nystatin can cause diarrhea and nausea. Nystatin can be combined with tetracycline to prevent monilial overgrowth caused by the destruction of bacterial microflora of the intestine during tetracycline therapy.



Pimaricin (natamycin), another polyene, is used topically to treat superficial mycotic infections of the eye. It is active against both yeasts and moulds.

Mechanism of Action: Binds to ergosterol in fungal membrane causing membrane to become leaky
Indications: Natamycin was first isolated from cultures of *Streptomyces natalensis*.
Disposition: Natamycin is supplied as a 5% ophthalmic suspension intended for the treatment of fungal conjunctivitis, blepharitis and keratitis.
Adverse Effects: Eye irritation, redness and swelling not present prior to use.

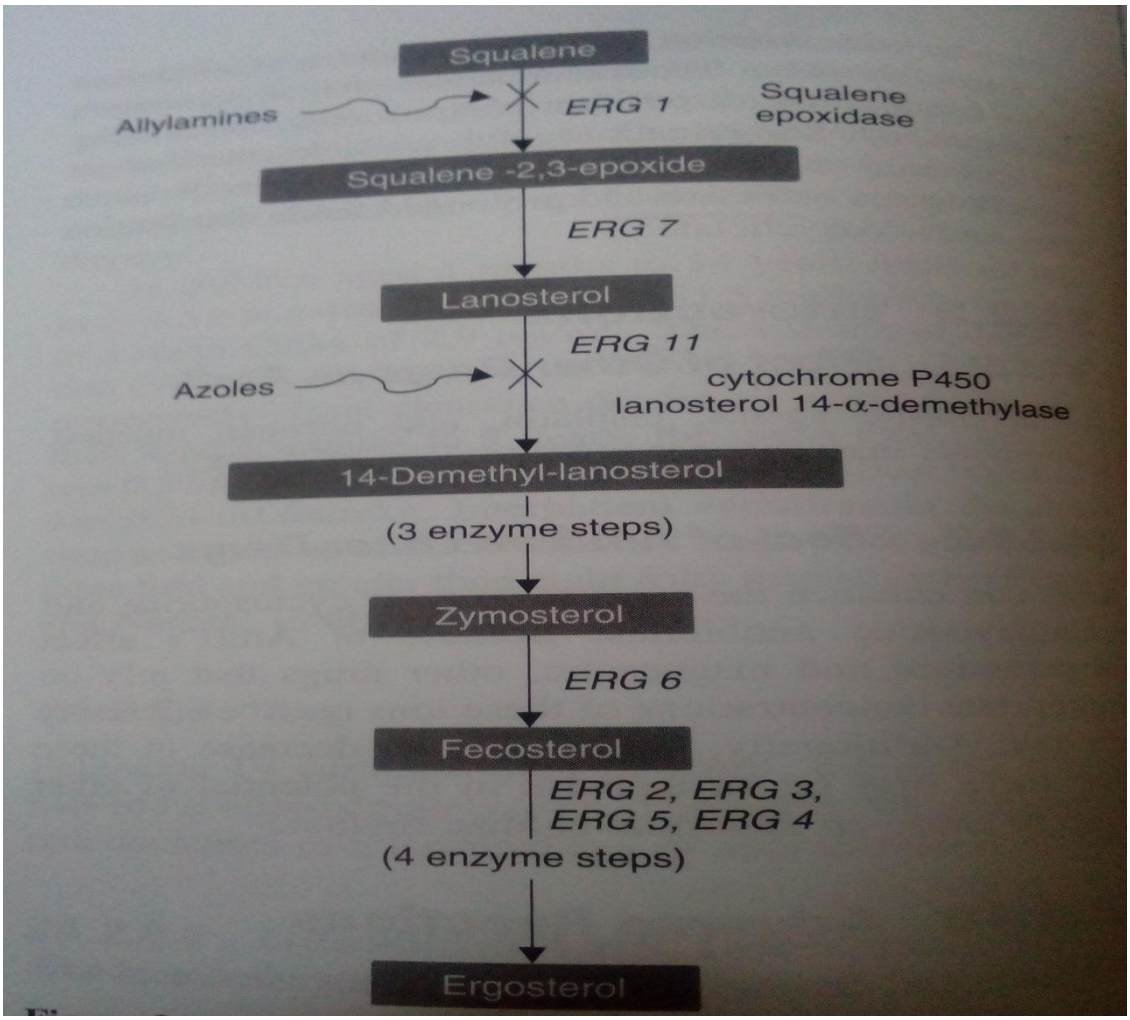
2- Azole Antifungal Drugs

The azole antifungal agents have five-membered organic rings that contain either two or three nitrogen molecules (the imidazoles and the triazoles respectively). The clinically useful imidazoles are clotrimazole, miconazole, and ketoconazole. Two important triazoles are itraconazole and fluconazole. Azoles, first developed in the 1980s, are the largest class of antifungal agents used today in clinical medicine. They include some topical agents but also systemic triazoles. Azoles are fungistatic drugs that inhibit ergosterol biosynthesis: they target 14-α-lanosterol demethylase (Erg11 or Cyp51), a cytochrome P-450 enzyme which catalyzes a key step in the ergosterol biosynthetic pathway.

Ketoconazole set the stage for the orally administered antifungal azoles. It can be administered both orally and topically and has a range of activity including infections due to *H. capsulatum* and *B. dermatitidis*, . It is also active against mucosal candidiasis and a variety of cutaneous mycoses, including dermatophyte infections, pityriasis versicolor, and cutaneous candidiasis. It is not indicated for treatment of aspergillosis or of systemic infections caused by yeasts.

Fluconazole is now routinely used to treat candidemia , and use in cryptococcosis and selected forms of coccidioidomycosis. Fluconazole can be administered either orally, or intravenously. More severe toxicity is unusual,

Itraconazole: This drug has become the standard treatment for lymphocutaneous sporotrichosis as well as for mild or moderately severe histoplasmosis, blastomycosis, and paracoccidioidomycosis. It is also effective in mild cases of invasive aspergillosis, some cases of coccidioidomycosis, and certain types of chromoblastomycosis. Despite poor CSF penetration, itraconazole can be used to treat some types of fungal meningitis, but it is not the drug of choice. Because of its high lipid solubility and protein binding, itraconazole blood levels tend to be low, but tissue levels are typically high.



FIG,Ergosterol biosynthetic pathway adapted from*Candida albicans*. Commonly used drugs in the allylamine and azole

Posaconazole The triazole posaconazole is available as an oral suspension and a tablet. An IV formulation will probably be available soon. This drug is highly active against yeasts and molds and effectively treats various opportunistic mold infections,

such as those due to dematiaceous (dark-walled) fungi (eg, *Cladophialophora* sp). It is the only oral azole effective against many of the species that cause mucormycosis. Posaconazole can also be used as fungal prophylaxis in neutropenic patients with various cancers and in bone marrow transplant recipients.

Voriconazole This broad-spectrum triazole is available as a tablet and an IV formulation. It is considered the treatment of choice for *Aspergillus* infections in immunocompetent and immunocompromised hosts. Voriconazole can also be used to treat *Scedosporium apiospermum* and *Fusarium* infections. Additionally, the drug is effective in candidal esophagitis and invasive candidiasis, although it is not usually considered a first-line treatment; it has activity against a broader spectrum of *Candida* sp than does fluconazole.

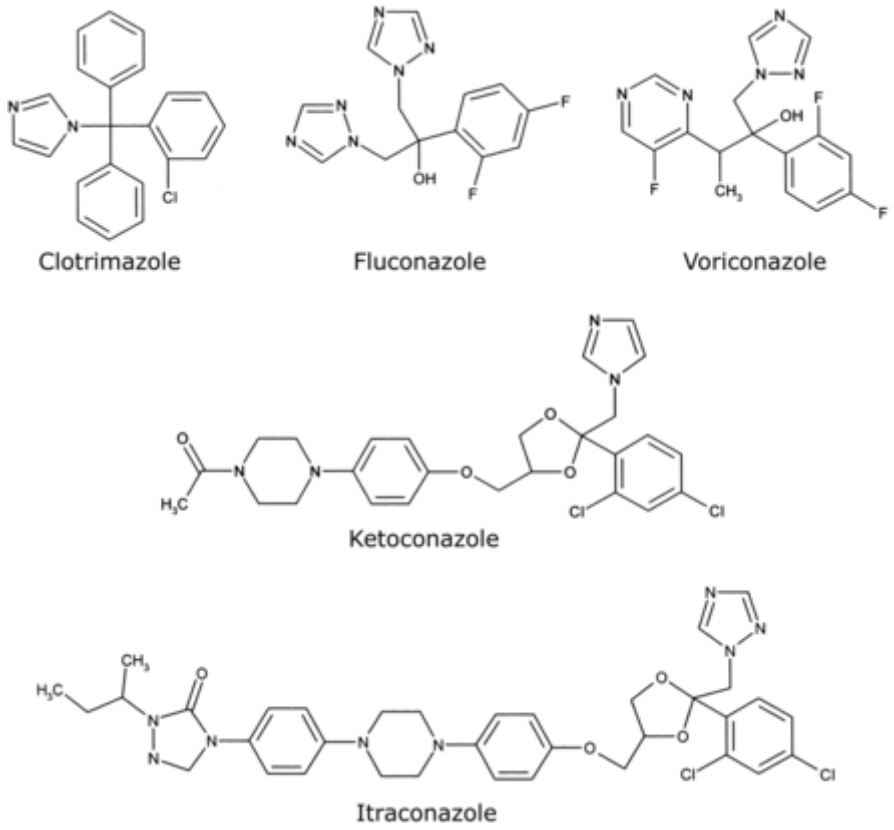


Fig.3: Chemical structures of medical azole antifungal agents. The chemical structures of clotrimazole (molecular weight [MW], 345), fluconazole (MW, 306), voriconazole (MW, 349), ketoconazole (MW, 531), and itraconazole (MW, 706),(Andrew *et al.*,2013)

MICONAZOLE is used for skin infections such as tinea pedis, tinea cruris and vulvovaginitis. It comes in cream, lotion, powder, spray liquid and spray powder .
ECONAZOLE is a topical cream applied to the skin to treat fungal infections including: tinea corporis, tinea pedis, tinea cruris, and superficial candidiasis.

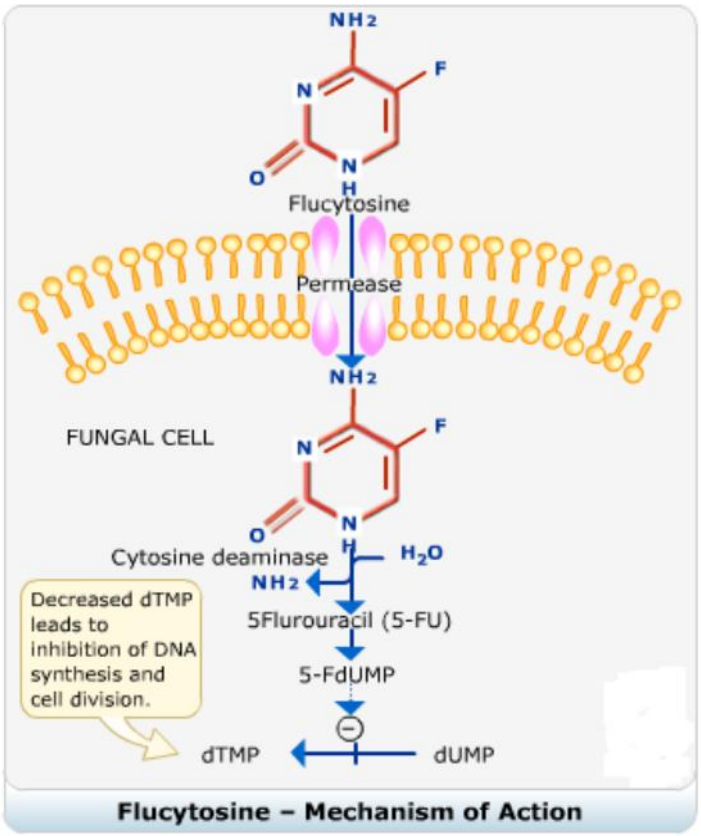
OXICONAZOLE is a cream or lotion applied to the skin in the treatment of tinea corporis, tinea pedis and tinea cruris.

SULCONAZOLE is a topical cream or solution to treat tinea corporis, tinea pedis and tinea cruris.

TIOCONAZOLE is a cream to treat tinea corporis, tinea pedis, tinea cruris and cutaneous candidiasis.
BUTOCONAZOLE is a cream suppository used to treat vulvovaginitis.
TERCONAZOLE is supplied as a cream or suppository to treat vulvovaginitis.

3- (5 –Fluorocytosine)

It inhibits both DNA and RNA synthesis via intracytoplasmic conversion to 5-fluorouracil. The latter is converted to two active nucleotides: 5-fluorouridine triphosphate, which inhibits RNA processing, and 5-fluorodeoxyuridine monophosphate, which inhibits thymidylate synthetase and hence the formation of the deoxythymidine triphosphate needed for DNA synthesis. As with other antimetabolites, the emergence of drug resistance is a problem. Therefore, 5-fluorocytosine is seldom used alone. In combination with amphotericin B it remains the treatment of choice for cryptococcal meningitis and is effective against a number of other mycoses, including some caused by the dematiaceous fungi and perhaps even by *C. albicans*.



4- Echinocandins

The echinocandins (i. e. caspofungin, micafungin and anidulafungin) . Echinocandins are actually the first class of antifungal drugs that act against a specific component of the fungal organisms – the cell wall - not present in mammalian (host) cells .These are a group of semisynthetic lipopeptide antibiotics whose mechanism of action is the specific and non-competitive inhibition of the 1,3-β-D-glucan synthase complex. This enzyme is critical for the synthesis of the key structural glucan polymers of the fungal cell wall, and its inhibition leads to depletion of cell wall glucan and lysis of fungal cells .Echinocandins display excellent fungicidal activity against most *Candida* spp. They are considered fungistatic against Aspergillus spp. and some other moulds, for which voriconazole and amphotericin B are generally preferred therapeutic options. However, the spectrum of action of echinocandins does not include Cryptococcus or other emerging pathogens. Because mammalian cells have no cell wall, the echinocandins have very few toxic adverse effects in humans.

5 -GRISEOFULVIN

GRISEOFULVIN is an antifungal produced from *Penicillium griseofulvin*. Therapy must continue until new tissue replaces old diseased tissue. When given orally, plasma-borne griseofulvin becomes incorporated into keratin precursor cells and

ultimately into kearatin that cannot support fungal growth. It is active in vitro against most dermatophytes and has been the drug of choice for chronic infections caused by these fungi (e.g., nail infections with *Trichophyton rubrum*) since it is orally administered and presumably incorporated into actively growing tissue. It is still used in such instances but is being challenged by some of the newer azole antifungal agents. The drug inhibits mitosis in fungi.
Mechanism of Action: Griseofulvin inhibits microtubule polymerization thus inhibiting the formation of the mitotic spindle.

6 -Potassium iodide

Potassium iodide given orally as a saturated suspension is uniquely used to treat cutaneous and lymphocutaneous sporotrichosis. This compound, interestingly, is not active against Sporothrix schenckii in vitro. It appears to act by enhancing the transepidermal elimination process in the infected host.

7- Allylamines

Two other classes of antifungal agents represent new additions to topical treatment of the dermatomycoses in Europe. The two allylamines (naftifine and terbinafine) inhibit ergosterol synthesis at the level of squalene epoxidase; one morpholene derivative (amorolfine) inhibits at a subsequent step in the ergosterol pathway. The allylamines have a more limited spectrum of activity than the azoles and triazoles and are only effective against dermatophytes. They are employed in the treatment of fungal infections of the skin and nails.
Mechanism of Action: These antifungal agents are reversible, noncompetitive inhibitors of the first step in ergosterol biosynthesis the conversion of squalene to squalene-2,3- epoxide by squalene epoxidase. The buildup of squalene in the cell membrane is toxic to the cell, causing pH imbalances and malfunction of membrane bound proteins.

TERBINAFINE comes as a tablet to take orally or as a topical cream It is used to treat fungal infections of the nails. Drug interactions: warfarin, antidepressant drugs, beta-blockers, proton pump inhibitors and drugs to suppress the immune system.

8- UNDECYLENIC ACID
Is widely used topically as the zinc salt in OTC preparations for topical treatment of infections by dermatophytes.
Mechanism of Action: This organic acid will interact non-specifically with components in the cell membrane. It can be used in concentrations up to 10% in solution, powder and emulsions. Traditionally used for athlete's foot (tinea pedis) although cure rates are low.