

## ANTI FUNGAL AGENTS:-

- Fungal infections have increased in incidence and severity in recent Years Fungal infection are also called as mycosis and it is 3types
- a) Superficial mycosis—it affect the skin,nail,scalp,mucous membrane
- b) subcutaneous mycosis—it infect the subcutaneous layer
- c) systematic mycosis—infection in deeper tissuse and organ
- The antifungal drugs fallintotwo groups:antifungal antibiotics and synthetic antifungals.

## CLASSIFICATION

- 1-systemic- Griseofulvin, Amphotericin-B, Flucytosine,ketoconazole, itraconazole,fluconazole
- 2-topical- nystatin,hamycin,candicidin

# ANTIFUNGALS

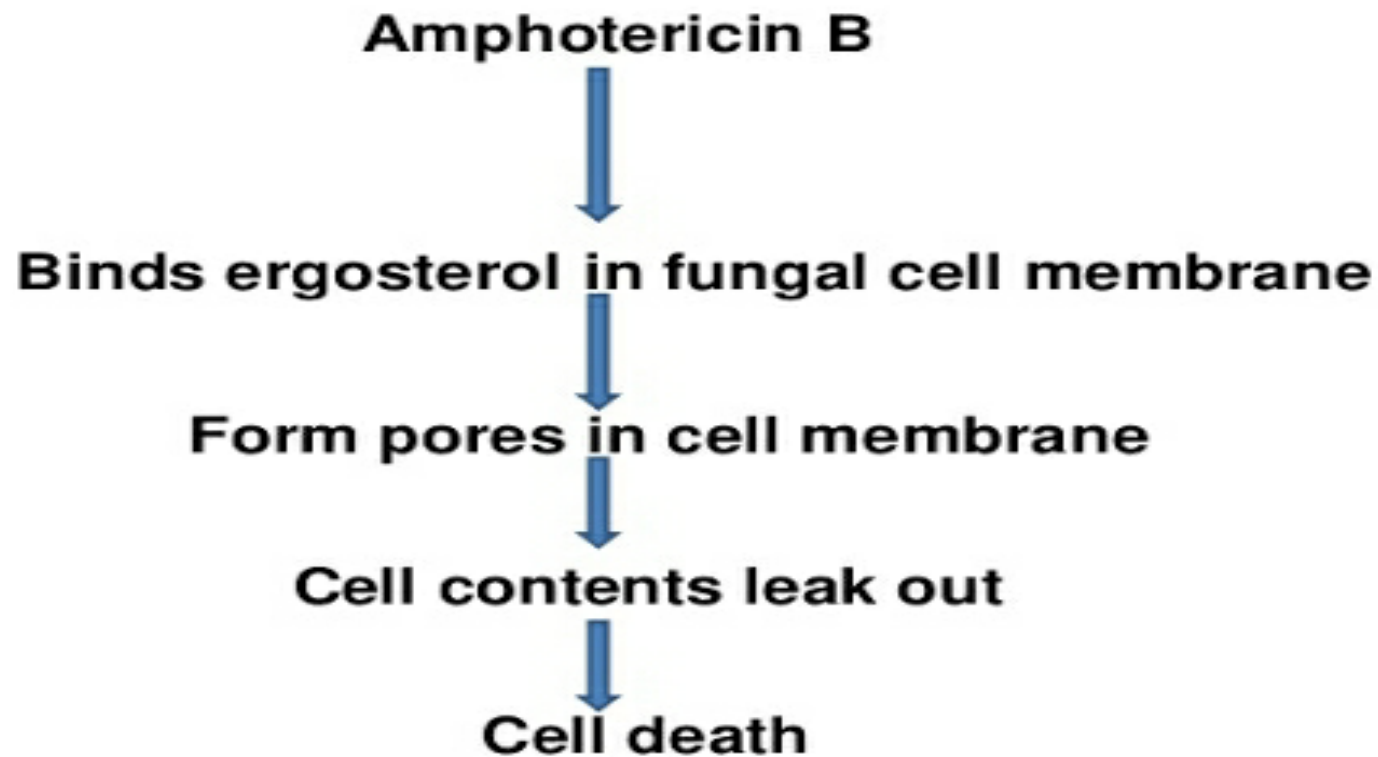


# 1. Antifungal antibiotics:-

## • AmphotericinB:-

- AmphotericinB is poorly absorbed from the gastrointestinal tract.
- The drug is widely distributed in tissues, but only 2-3% of the drug reached in CSF, Thus occasionally used for Intrathecal therapy for certain types of fungal meningitis.
- Mechanism of Action: AmphotericinB binds to ergosterol (a cell membrane sterol) and alters the permeability of the cell by forming amphotericinB-associated pores in the cell membrane.
- The pore allows the leakage of intracellular ions and macromolecules, eventually leading to cell death.

# Mechanism of action



## Adverse Effects:

- The toxicity of amphotericin B which may occur immediately or delayed include fever, chills, muscle spasms, vomiting, headache, hypotension (related to infusion), renal damage associated with decreased renal perfusion (are reversible) and renal tubular injury (irreversible).
- Anaphylaxis, liver damage, anemia occurs frequently.
- Antifungal Activity: Amphotericin B is a broad-spectrum antifungal agent. It has activity against yeasts including *Candida albicans* and *Cryptococcus neoformans*; molds, *Aspergillus fumigatus*.
- Clinical Use: Amphotericin B remains the drug of choice for nearly all life-threatening mycotic infections. Used as the initial induction regimen for serious fungal infections (immunosuppressed patients, severe fungal pneumonia, and cryptococcal meningitis with altered mental status)

## Nystatin:-

- Nystatin has similar structure with amphotericin B and has the same pore-forming mechanism of action. It is too toxic for systemic use and it is used topically.
- It has not absorbed from skin, mucous membranes, or the gastrointestinal tract. Nystatin is active against most *Candida* species and is most commonly used for suppression of local candidal infections.
- Nystatin is used in the treatment of oropharyngeal thrush, vaginal candidiasis.

## Griseofulvin

- It is a fungi static and used is in the treatment of dermatophytosis.
- Absorption is improved when it is given with fatty foods. Griseofulvin is deposited in newly forming skin where it binds to keratin, protecting the skin from new infection.
- It must be administered for 2-6 weeks for skin and hair infections to allow the replacement of infected keratin by the resistant structures.
- Nail infections may require therapy for months to allow regrowth of the new protected nail and is often followed by relapse.
- **Adverse effects**: -include an allergic syndrome much like serum sickness, hepatitis, and drug interactions with warfarin and phenobarbital.
- Griseofulvin has been largely replaced by newer antifungal medications such as itraconazole and terbinafine.

## 2.Synthetic Antifungal Agents

### Flucytosin

- .Its spectrum of action is much narrower than that of amphotericinB.It is well absorbed orally.It is poorly protein-bound and penetrates well into all body fluid compartments including the CSF.
- It is eliminated by glomerular filtration.
- Toxicity is more likely to occur in AIDS patients andi In the presence of renal insufficiency.

### Clinical Use:

- -Active against Cryptococcus neoformans, and some Candida species chromoblastomycosis.
- Clinical use at present is confined to combination therapy,either with amphotericinB for Cryptococcal meningitis orwith itraconazole for chromoblasto mycosis.



# Flucytosine (5- Fluororcytosine; 5-FC)

- Transported into fungal cells by enzyme cytosine deaminase, where it gets converted into 5-Fluorouracil (5-FU)
- 5-FU metabolised to 5- Fluorodeoxyuridine monophosphate (5-FUMP)
- 5- FUMP is a competitive inhibitor of thymidylate synthetase, blocks the formation of thymidine monophosphate (inhibit DNA Synthesis)



## Adverse Effects:-

- Bonemarrow toxicity with anemia,leukopenia,and thrombocytopenia are the most common adverse effects,with derangement of liver enzymes occurring less frequently.

## Azoles

- Azoles are synthetic compounds that can be classified as imidazoles and Triazoles
- The imidazoles consist of ketoconazole ,miconazole,and clotrimazole .
- The triazoles include itraconazole and fluconazole.



## Ketoconazole

- Ketoconazole is less selective for fungal P450 than itraconazole, fluconazole

### Clinical use:

- It has limited use because of the drug interactions, endocrine side effects, and of its narrow therapeutic range.

### USE

- Ketoconazole is used in Treatment of mucocutaneous candidiasis
- It is also used in the treatment of seborrheic dermatitis. (Topical/shampoo).

### P.K

- \*well absorbed orally
- Oral formulation that is best absorbed at a low gastric pH.
- \* Bioavailability decrease with antacid, ppi, food
- \* Doesn't cross BBB, Metabolised by liver and excrete in urine and faeces

### S.E

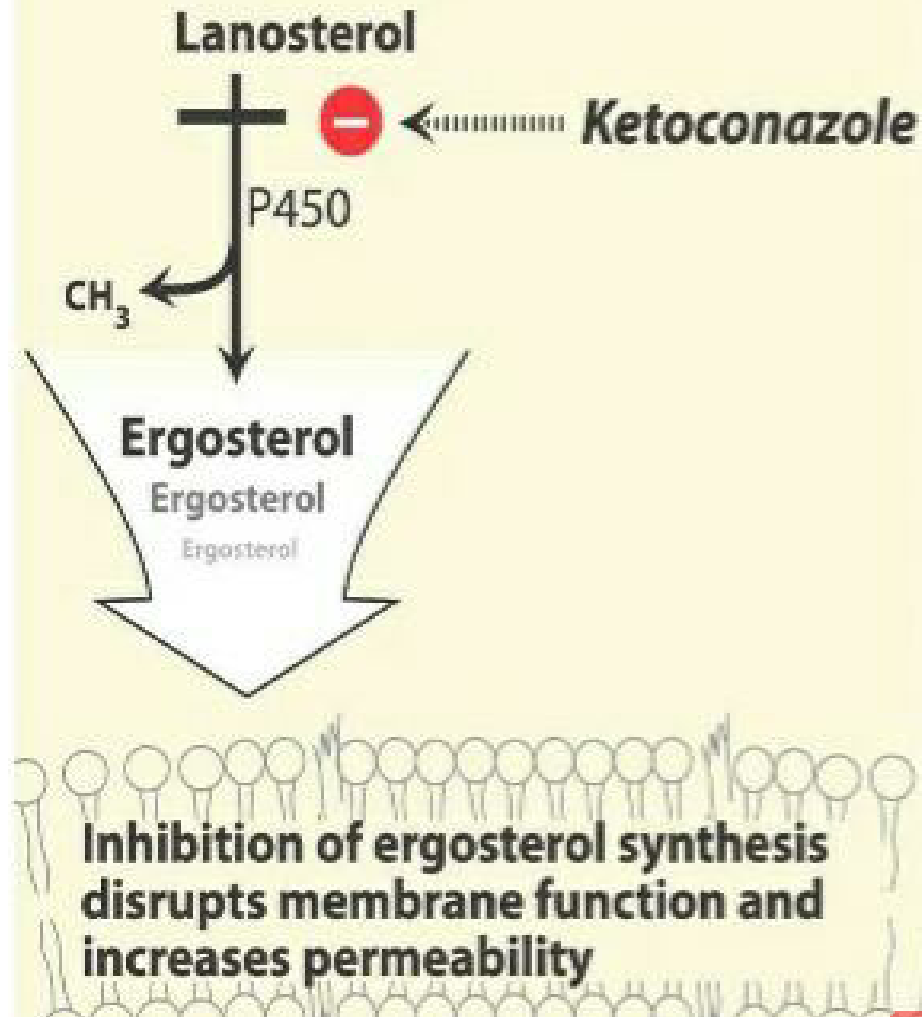
- \*menstrual irregularities (dysmenorrhea) \* loss of libido (sexual desirelessness) \* Impotence (erectile dysfunction)



## Clotrimazole and miconazole:-

- These are available over-the counter and are often used for vaginal candidiasis.
- Oral clotrimazole troches are available for treatment of oral thrush and are a pleasant-tasting alternative to nystatin.
- In cream form, both agents are useful for dermatophytic infections, including tinea corporis,
- Tinea pedis, and tinea cruris. Absorption is negligible, and adverse effects are rare.

# MOA OF AZOLES



Azoles are predominantly fungistatic. They inhibit C-14  $\alpha$ -demethylase (a cytochrome P450 enzyme), thus blocking the demethylation of lanosterol to ergosterol the principal sterol of fungal membranes.

This inhibition disrupts membrane structure and function and, thereby, inhibits fungal cell growth.

[Note: In addition to blocking fungal ergosterol synthesis, the drug also inhibits human gonadal and adrenal steroid synthesis, leading to decreased testosterone and cortisol production. In addition, ketoconazole inhibits cytochrome P450]

## Triazoles

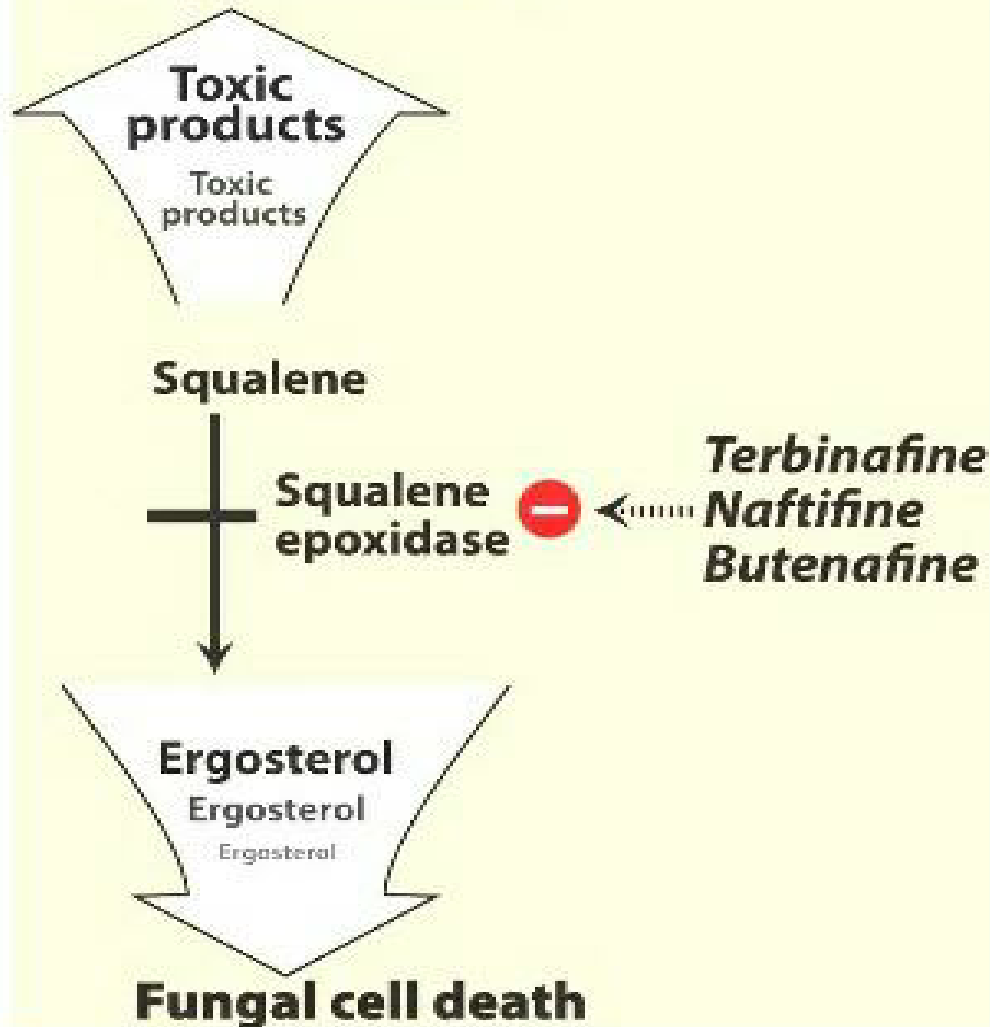
### Itraconazole

- Itraconazole is available in an oral formulation and its absorption is increased by food and by low gastric pH. Undergoes extensive hepatic metabolism.
- It is the azole of choice in the treatment of dermatophytoses and onychomycosis and is the only agent with significant activity against *Aspergillus* species.

### Fluconazole

- Fluconazole has good cerebrospinal fluid penetration. Can be given by the intravenous or the oral route.
- Fluconazole has the least effect on hepatic microsomal enzymes. Thus, has a wide therapeutic window. Fluconazole is the azole of choice in the treatment and secondary prophylaxis of cryptococcal meningitis.
- It is also effective for mucocutaneous.

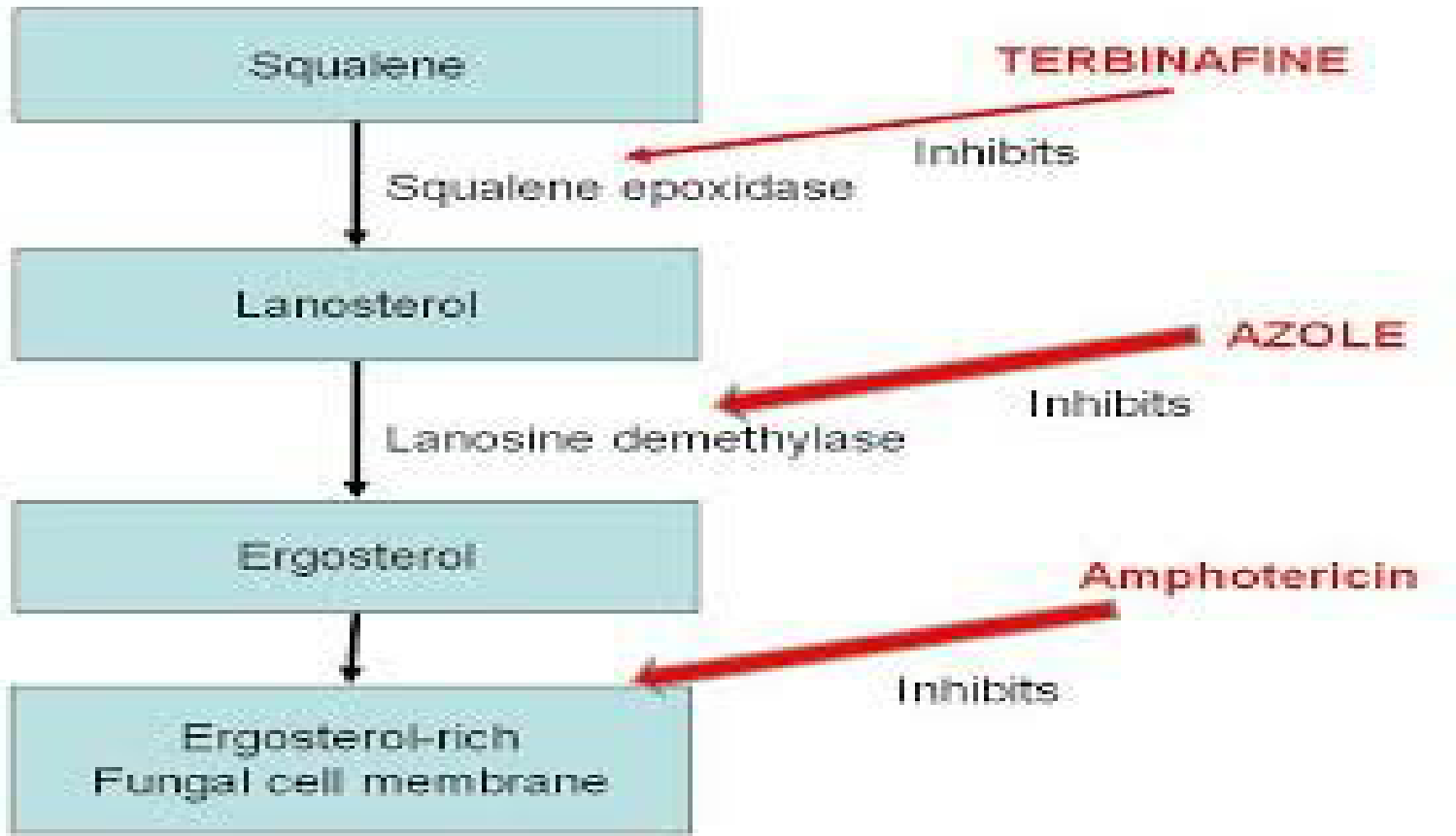
## Fungal cell death



Terbinafine inhibits fungal squalene epoxidase, thereby decreasing the synthesis of ergosterol .

This plus the accumulation of toxic amounts of **squalene** result in the death of the fungal cell.

[Note: Significantly higher concentrations of terbinafine are needed to inhibit human squalene epoxidase, an enzyme required for the cholesterol synthetic pathway.]







Aspergillus  
fumigatus Infection

Aspergillus flavus  
Infection





## CRYPTOCOCCUS INFECTIONS



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**Picture of Histoplasmosis**



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## HISTOPLASMA INFECTIONS

