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Antifungal drugs

Introduction :Fungal organisms

1-Eukaryotic

2- Infectious diseases caused by fungi are called mycoses

3-Fungi are have rigid cell walls composed largely of chitin (a polymer of N-acetylglucosamine) rather than peptidoglycan (a characteristic component of most bacterial cell walls).

4- The fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian

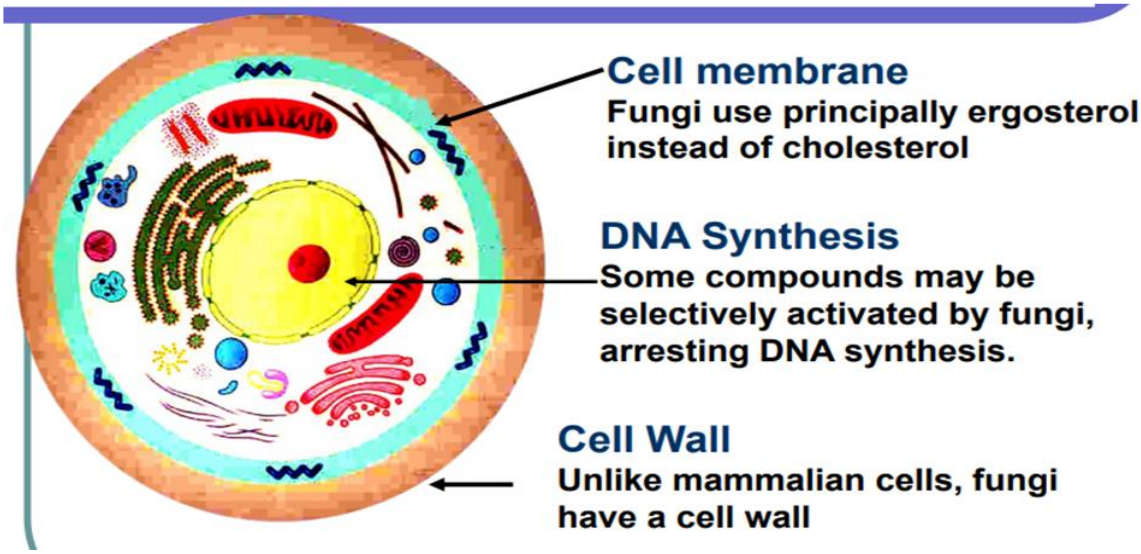

Figure 1 : Fungal organism

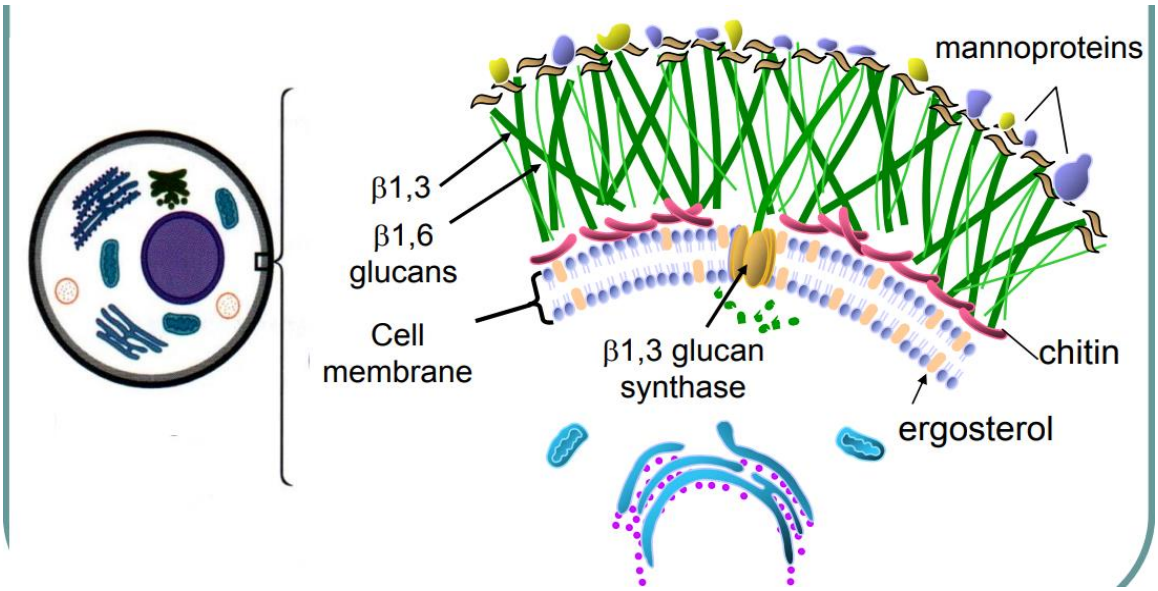

Figure 2 : Fungal organism

- **Antifungal Drugs**
- **FUNGAL INFECTIONS (MYCOSES)**
- 1-**Superficial**
- a-Dermatomycosis : Trichophyton spp., Microsporum spp
- b-Candidiasis – skin, mouth, vagina oropharynx
- 2-**Deep/ systemic**
- **a-Blastomyces**
- **b- Candida Coccidiodes**
- **c-Cryptococcus**
- **d-Histoplasma**

Table 52-1. Some common fungal infections and their sensitivi

Organism	Principal disease(s)
Yeasts	
Cryptococcus neoformans	Meningitis
Yeast-like fungus	
Candida albicans	Thrush, systemic candidiasis
Filamentous fungi	
Trichophyton spp. *Epidermophyton floccosum* *Microsporum* spp.	All these organisms cause skin and nail infections and are referred to as tinea or 'ringworm'
Aspergillus fumigatus	Pulmonary aspergillosis
Dimorphic fungi	
Histoplasma capsulatum	Histoplasmosis
Coccidioides immitis	Coccidiomycosis
Blastomyces dermatides	Blastomycosis

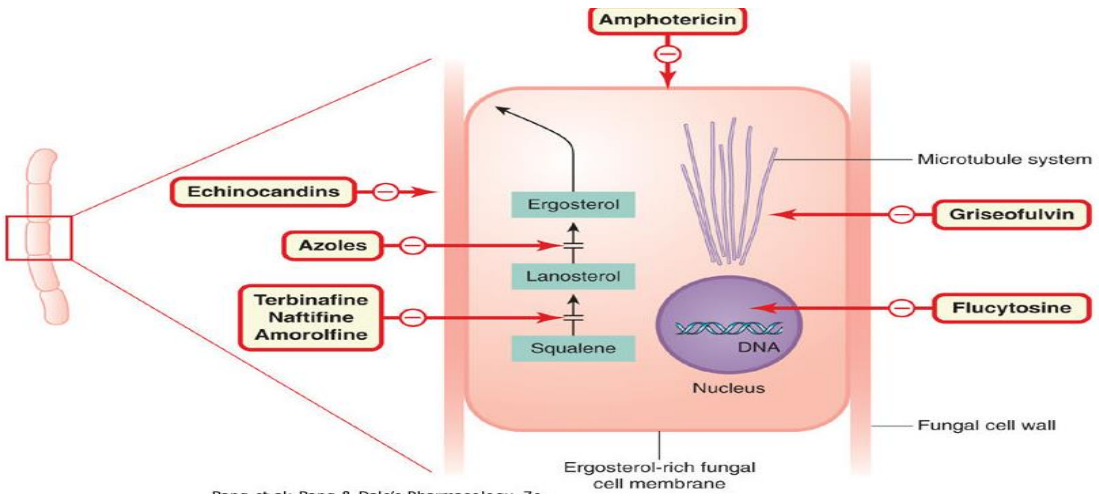

Figure :3:General mechanism of action antifungal drugs

1-Griseofulvin

Griseofulvinis a fungistatic antibiotic produced by Penicillium griseofulvin

A-Mechanism of action

Disrupts mitotic spindle during metaphase by interacting with fungal microtubules (fungal mitosis) sufficient to inhibit growth of fungi (Fungistatic), preventing them from invading .

Spectrum of activity Griseofulvin's

Its activity is limited to organisms causing dermatophytosis:

1-Microsporum spp.

2-Trichophyton spp.

3- Epidermophyton

Pharmacokinetics

1-Griseofulvin distributes to the keratin of skin, hair, and nails and can be detected in the stratum corneum within hours of administration.

2-Half-life at the site of action — the stratum corneum — is prolonged because the drug is bound tightly to keratinocytes and remains in the skin until these cells are shed.

3-Thus, new hair or nail growth is first to become free of disease as keratin infected by fungus is replaced by new cells

Clinical Use

Often, at least 4 weeks are needed for successful therapy for wring worm, and some patients require 3 months (or more) of continuous therapy

Doses in cattle: 7.5–10 mg/kg for 7 to 35 days.

Adverse Effects

The most serious adverse effects associated with griseofulvin occur in cats and include

1-leukopenia.

2-Anemia.

3-Increased hepatic enzyme activity .

4-Neurotoxicosis .

2-Amphotericin B

Amphotericin B is a naturally occurring polyene macrolide antibiotic produced by Streptomyces nodosus

Mechanism of Action :

1-its fungicidal effect .

2-The major action of amphotericin B is to bind ergosterol in the fungal plasma cell membrane.

3-Making the membrane more permeable and resulting in leakage of cell electrolytes and cell death.

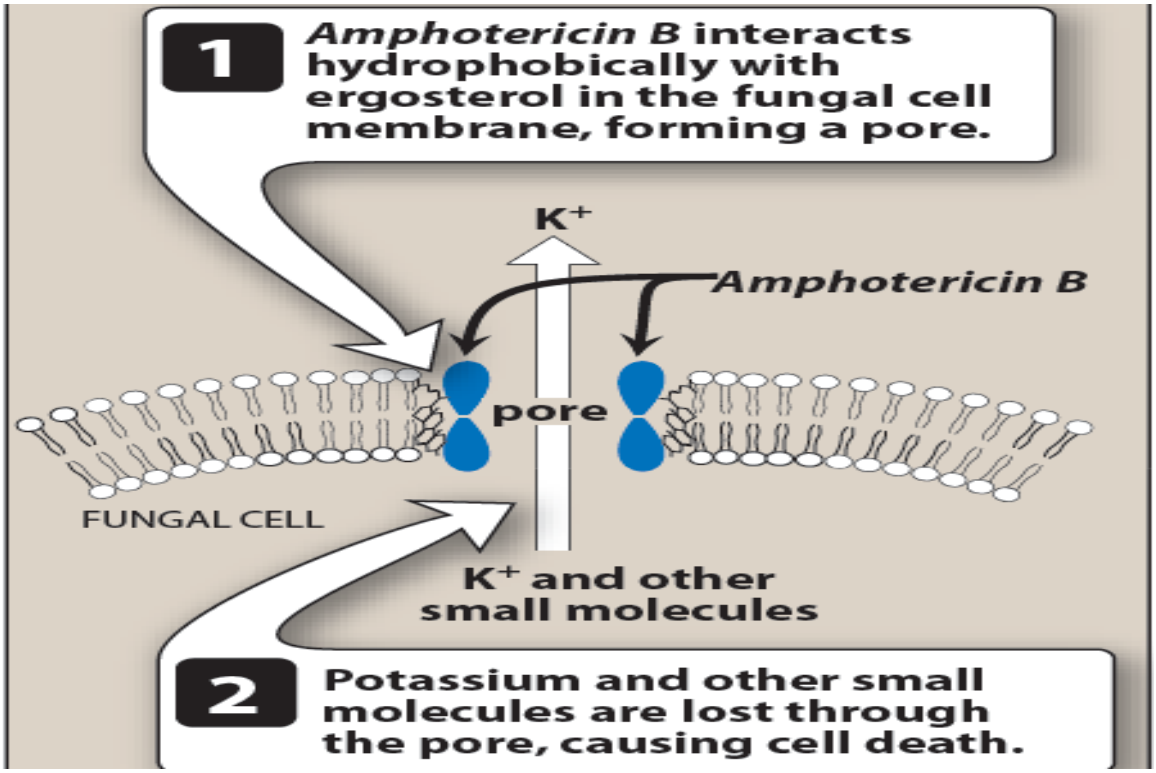

Figure 4 : Mechanism of action of amphotericin B

Note: Postfungal effect :
An antifungal effect persists after drug concentrations have declined. This property allows for intermittent therapy (e.g., every other day in dogs).

Spectrum of Activity Amphotericin B
Susceptible fungi include Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, Candida spp., and various species of Aspergillus

Note:
During infusion, it should be mixed with 5% dextrose solution because it will precipitate if added to an electrolyte containing solution (e.g., lactated Ringer's solution).

Adverse Effects:

The most important clinical toxicosis associated with amphotericin B therapy is nephrotoxicity

3-Flucytosine

Flucytosine (5-fluorocytosine) is a synthetic antifungal agent available as an oral preparation.
Mechanism of action
1-Flucytosine must be taken into the fungal cell by cytosine permease

2-Converted to the active form, 5-fluorouracil (5-FU),which inhibits thymidylate synthetase

3- Inhibition of DNA synthesis

3-Flucytosine

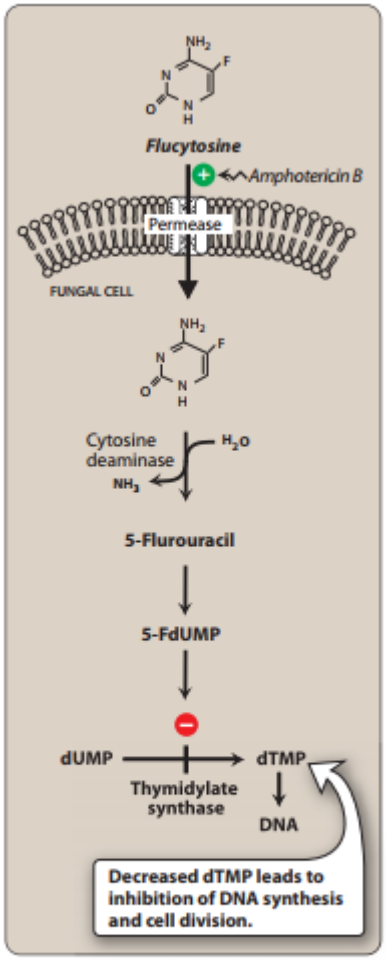

Figure 35.6
Mode of action of *flucytosine*. 5-FdUMP = 5-fluorodeoxyuridine 5'-monophosphate; dTMP = deoxythymidine 5'-monophosphate.

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Note:

Combination therapy using **amphotericin B** and **flucytosine** has been shown to be synergistic against cryptococcal meningitis.

1-One explanation of this synergism involves the membrane-permeabilizing effects of amphotericin B facilitating flucytosine's entrance into the cell cytoplasm.

2-Advantages of this combination include a reduction in the amphotericin B dose, thereby limiting nephrotoxicity

Adverse effects of flucytosine

The Adverse effects of flucytosine result from metabolism (possibly by intestinal flora) to the toxic antineoplastic compound fluorouracil .Its may induce reversible neutropenia, thrombocytopenia,and dose-related bone marrow depression .

Cutaneous and mucocutaneous eruptions have been observed with use of flucytosine in dogs and it is not recommended to be used in dogs for this reason

4-Azole Antifungal Drugs

Properties azole antifungal drugs

1- High safety profile.

2-A broad spectrum of activity .

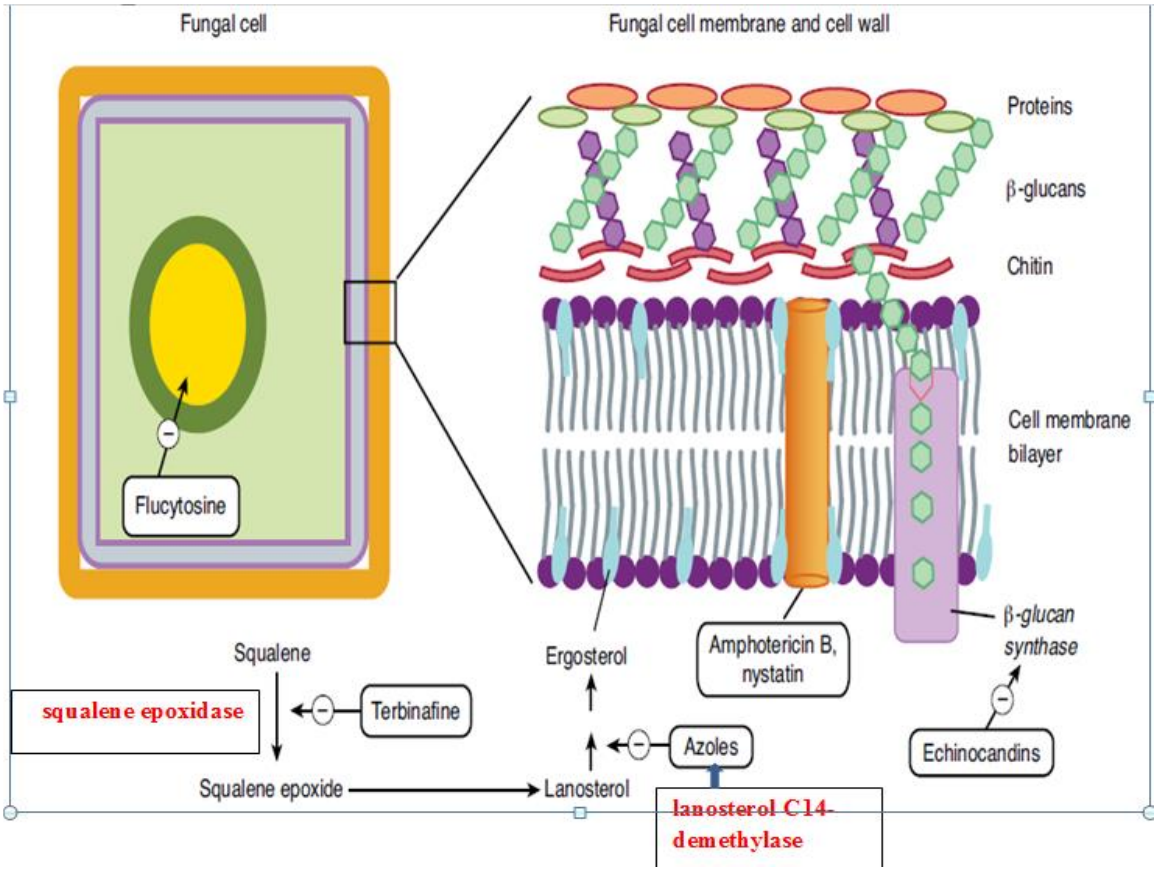
3-Available in topical, oral, and intravenous formulations

Mechanism of Action azole

1-Azole drugs are fungistatic .

2- All azoles exert their antifungal effect on the cell membrane of fungi by inhibiting synthesis of the ergosterol by Inhibition of the P450–dependent lanosterol C14-demethylase enzyme

3-Results in depletion of ergosterol and fungal cell death results from disruption of the cell membrane .



Types of azole Antifungal

1- Triazoles

A-Less effect on mammal sterol synthesis

B- Longer elimination

(-Traconazole ,Fluconazole , Voriconazole , Posaconazole) •

2-Imidazoles

A-More endocrine adverse effects .

B-Affect mammal sterol synthesis Imidazole .

(Ketoconazole • Clotrimazole • Enilconazole • Miconazole)

A-Fluconazole

Fungistatic triazole(azole) compound.

1-Oral .

2-Parenteral antifungal particularly useful for CNS infections.

Pharmacokinetics Fluconazole

1- Rapidly and nearly completely absorbed (90%) after oral administration.

2- Gastric pH or the presence of food, do not appreciably alter fluconazole's oral bioavailability.

3-It has low protein binding .

4-Widely distributed throughout the body and penetrates well into the CSF, eye, and peritoneal fluid.

5-Eliminated primarily via the kidneys and achieves high concentrations in the urine.

Spectrum of Activity Fluconazole

Activity against

1- Dermatophytes.

2-Systemic fungi .

3-Yeasts, including

A-Candida.

B-Coccidioides.

C-Cryptococcus spp (cryptococcal meningitis) .

Clinical Uses

Fluconazole is effective against dermatophytes, yeasts, and a variety of systemic fungi. In dogs, cats, horses, and exotic animals .

Adverse effects

1-Adverse effects have not been reported from fluconazole administration.

2-Compared to ketoconazole, it has less effect on endocrine function.

3-Increased liver enzyme concentrations and hepatopathy are possible.

B-Clotrimazole

Clotrimazole is an imidazole antifungal. It is limited to topical use.

Clinical uses

1-In veterinary medicine, it has been used for treatment of nasal aspergillosis in dogs following infusion of a 1% solution

2-Clotrimazole can be found in combination with gentamicin sulfate and betamethasone valerate for the treatment of otitis externa .

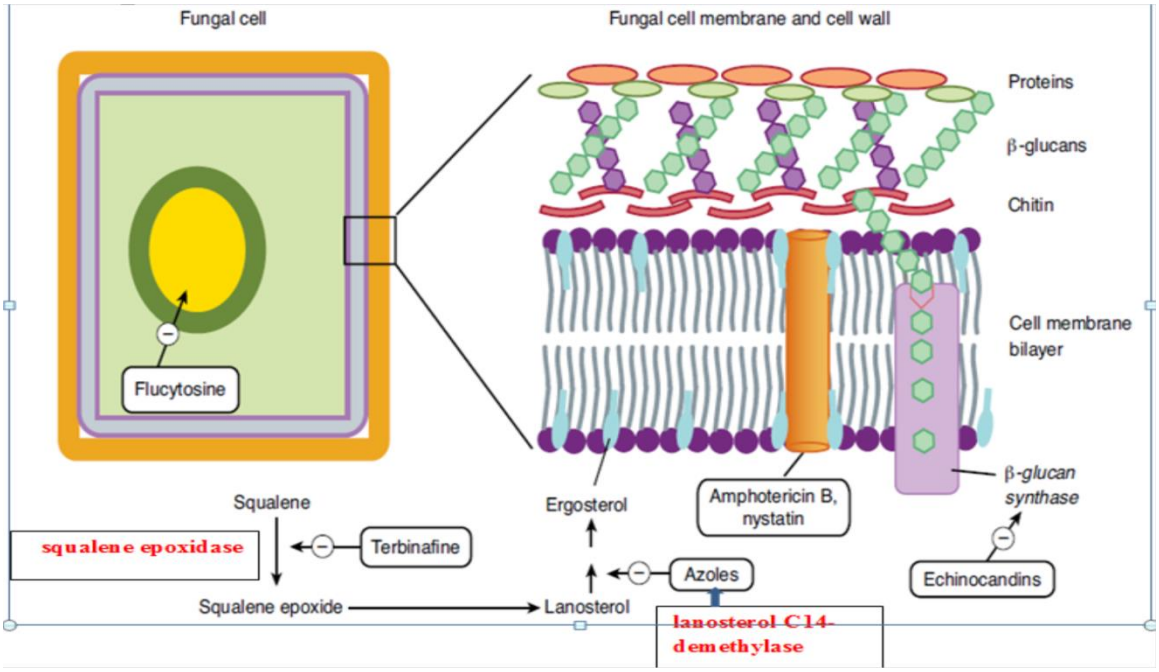
5-Terbinafine

Terbinafine is a highly fungicidal agent. It is a synthetic drug of the allylamine class .

Mechanism of action of terbinafine

1-Inhibits squalene epoxidase to decrease synthesis of ergosterol.

2-Fungal cell death results from disruption of the cell membrane



Spectrum of activity:

Terbinafine is active against

1-Yeasts .

2-Dermatophytes (Trichophyton spp., Microsporum spp)

3-Aspergillus spp.

4-Cryptococcus neoformans, Sporothrix schenckii,

5-Histoplasma capsulatum, Candida .

it was more effective than griseofulvin for treating dermatophytes .

Terbinafine is available as

1- 1% Topical cream .

2- 125 and 250 mg Tablets.

3-0.2% Solution for ophthalmic use .

6-Nystatin (Mycostatin®)

1-A polyene antifungal that is limited to topical use due to systemic toxicity.

2-Nystatin has a mechanism of action similar to that of amphotericin B.

3-Nystatin is not absorbed well from the gastrointestinal tract; therefore, it can be given orally as a "topical" treatment for oral and intestinal candidiasis, particularly in exotic animal species .

4- In veterinary medicine, it is most commonly used in combination with antibiotics (neomycin) and antiinflammatory (triamcinolone) drugs in ointments .

7-Echinocandins

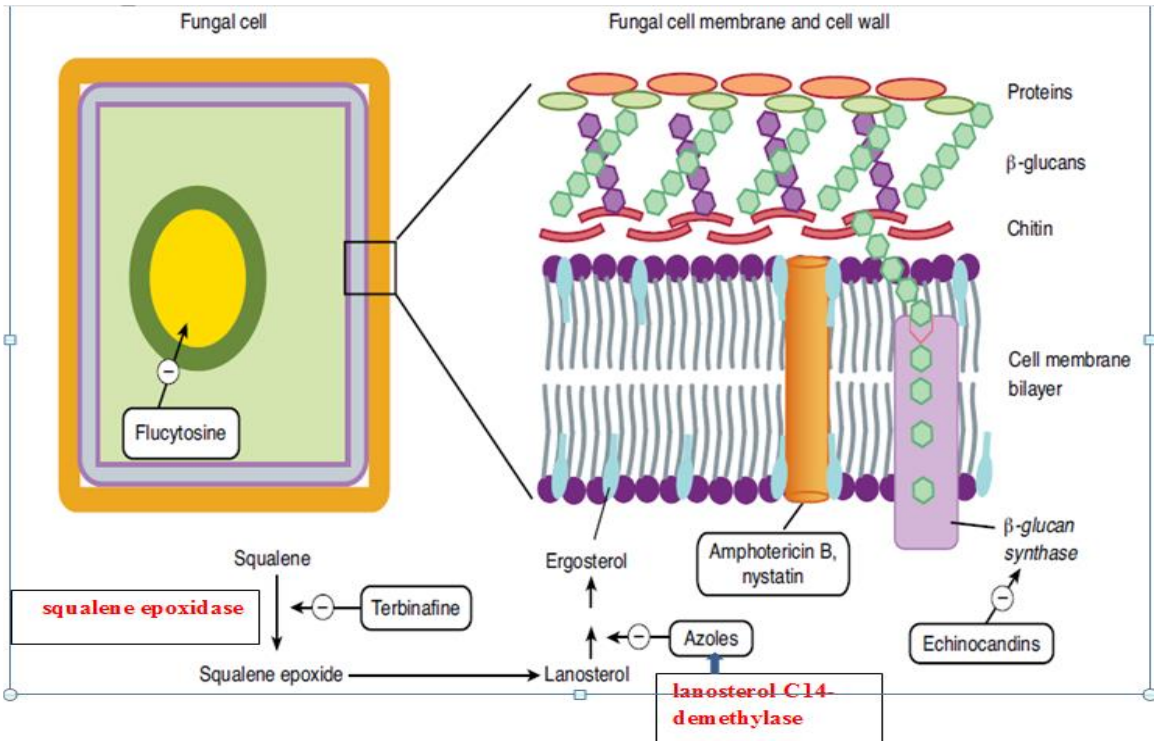
Caspofungin Acetate

Mechanism of action

1-Bind β-1,3 glucan synthase .

2-Inhibit synthesis of β-1,3 glucan polymers

3-Inhibit cell wall synthesis .



Clinical uses

Parenteral (IV)antifungal that has potential for treating

1-Invasive aspergillosis .

2-Disseminated candidal infections in companion animals .

Adverse Effects

1-Intravenous site reactions (pain, redness, phlebitis) have occurred.

2-Hepatic dysfunction has been reported but frequency is unknown