# Antifungals (Antifungal drugs)

These are drugs which are used for control of many of the fungal organisms that cause superficial fungal skin infections such as ring worm and deep or systemic fungal infections within the body such as Histoplasmosis, Blastomplasmosis, Cryptococcosis, Coccidiomycosis, Candidiasis, Sportotrichosis and Aspergillosis.

# FUNGAL INFECTIONS (MYCOSES)

- Superficial
- Deep/ systemic

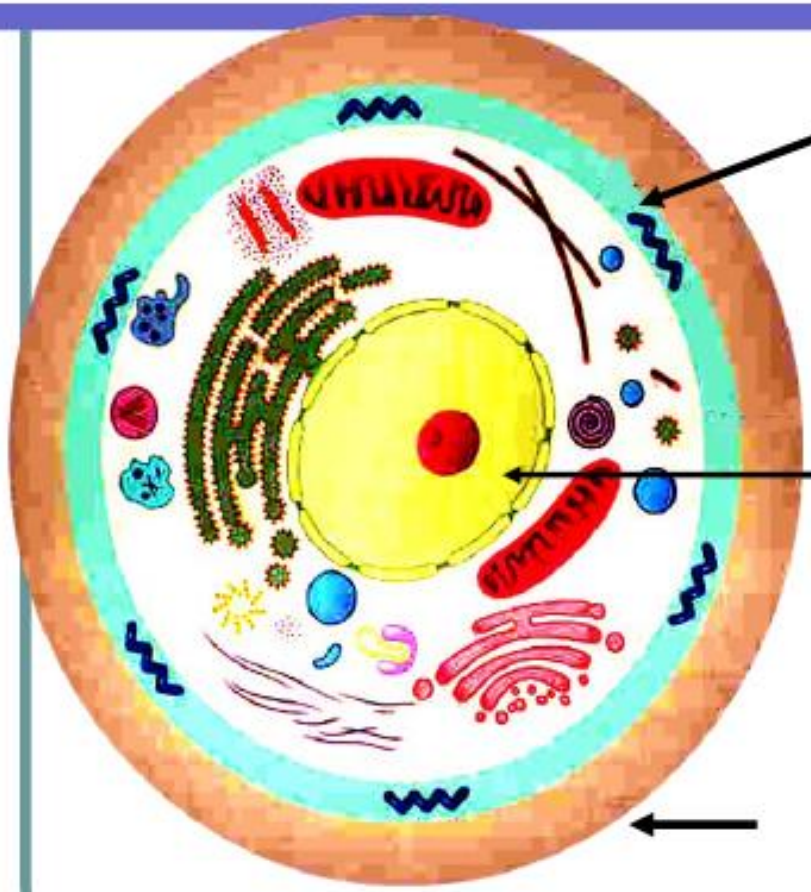
# Fungal infections (Superficial)

- Dermatomycosis (bcc cup)
  - Tinea pedis (athlete's foot)
  - Tinea corporis (skin ringworm)
  - Tinea cruris (groin)
  - Tinea capitis (scalp)
  - Tinea unguium (nails)
  - Tinea barbae (beard)
  - Tinea mannum(hand)
- Candidiasis – skin, mouth, vagina oropharynx

# DEEP MYCOSES

- aspergilus
- Blastomyces
- Candida
- Coccidiodes
- Cryptococcus
- Histoplasma

# What are the targets for antifungal therapy?



## Cell membrane

Fungi use principally ergosterol instead of cholesterol

**Nystatin, Clotrimazol, Amphotericin B:**

## DNA Synthesis

Some compounds may be selectively activated by fungi, arresting DNA synthesis.

**Flucytosine: Griseofulvin**

## Cell Wall

Unlike mammalian cells, fungi have a cell wall

**Classification:**

**A- Topical antifungals:**

They include the following groups:

1- Polyene antibiotics:

**Nystatin:**

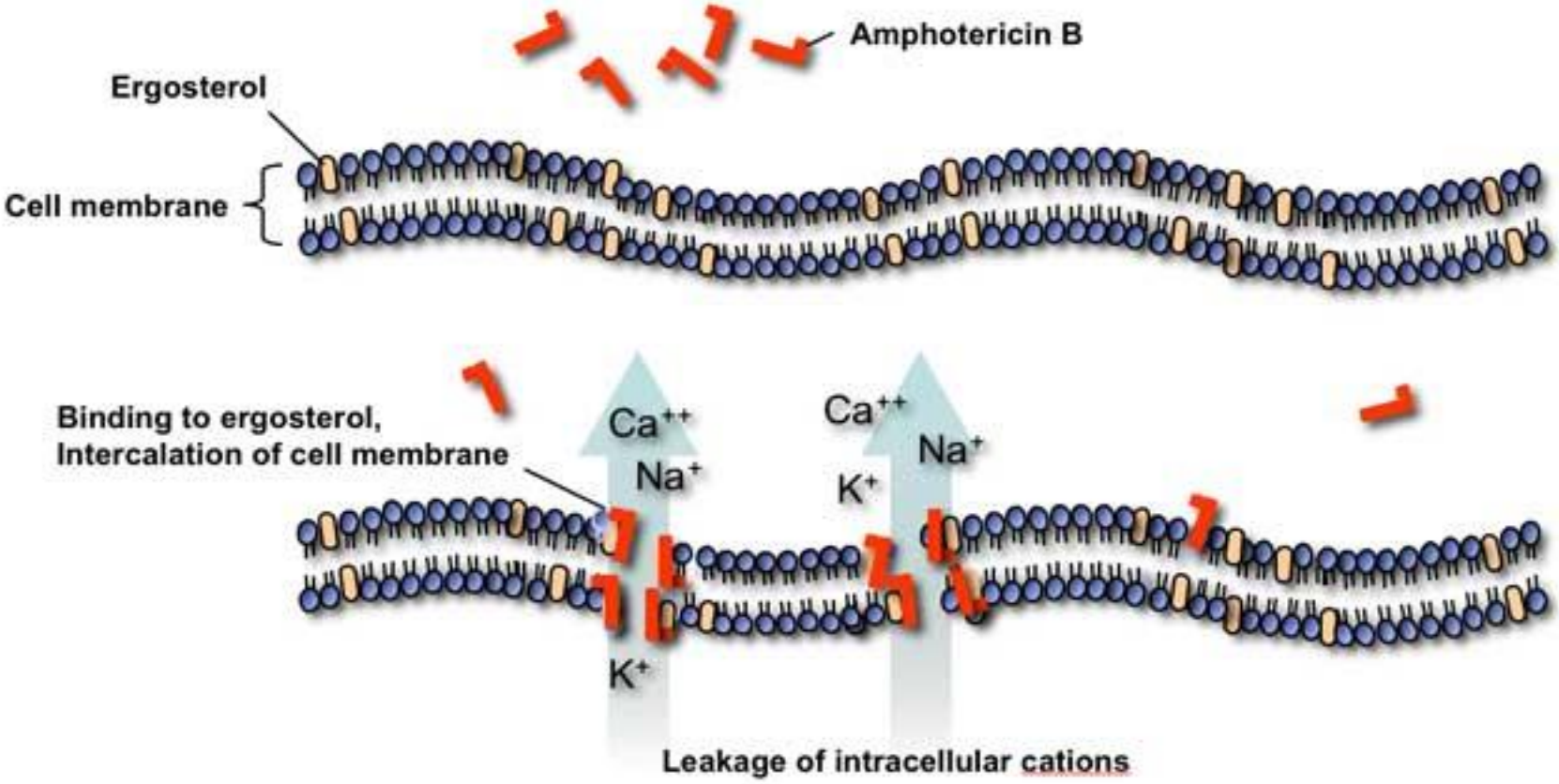
It is a Polyene antifungal antibiotic produced by *Streptomyces noursi*

**Mechanism of action: (**It is fungicidal at concentration about 4 times MIC)

Like amphotericin, it binds to ergosterol within the fungal cell membrane resulting in depolarization of the membrane and the formation of pores altering the membrane permeability.

The pores permit leakage of intracellular contents.

It exhibits concentration dependent killing.


Amphotericin B
Ergosterol
Cell membrane
Binding to ergosterol,
Intercalation of cell membrane
Ca++
Na+
Ca++
Na+
K+
K+
Leakage of intracellular cations

**Spectrum of activity:**

1- It is active against a variety of fungal infection, but clinicaly used against topical and G I T Candida infections.

2- It is also active against Cryptococcus and some Dermatophytes.

**Uses:**

1- It is used for treatment of Candida infections in dogs, cats and birds.

2- In the treatment of bovine yeast mastitis, the recommended dose is 300,000 units/quarter on 3 occasions as a single daily dose; the drug can be diluted in saline to 5,000 units/ml and 50 ml administered.

**Natamycin:**

Natamycin is a fungicidal polyene antibiotic derived from *Streptomyces natalensis* with action against the fungal cell membrane.

1- It is a broad spectrum antifungal effective against filamentous fungi and yeast.

**Therapeutic uses:**

1- It is used for treatment of keratomycosis and fusarium infections.

2- By local application, it is used for treatment of ring worm in cattle and horses, in the udder for yeast mastitis, and on the eyes for mycotic keratitis.

**NB:** Total-body spraying or sponging with Natamycin suspension is effective in the treatment of ringworm in cattle and horses. It is important that all grooming utensils be thoroughly cleansed or immersed in the Natamycin suspension, which should be prepared in plastic or galvanized containers.

3- Natamycin has been used successfully to treat cows with *Candida* mastitis (20 ml of a 2.5% solution, or 10 ml of a 5% solution, infused into the affected udder quarter once daily for 3 days).

4- Natamycin is used successfully to treat filamentous fungal keratitis in horses, and is the drug of choice for this purpose.

**NB:** A recommended treatment is one drop of a 5% suspension every 1 or 2 hours, decreasing to 6 or 8 times daily after a few days.

# 2- Imidazole derivatives:

## Clotrimazole:

Clotrimazole is a broad-spectrum antifungal agent reserved for topical administration.

## Mechanism of action:

- It acts by binding with the cell membrane phospholipids → causing leakage of essential constituents of the cell.

## Efficacy:

- It is effective against Aspergillus, Candida, Microspora.
- It is fungistatic at lower concentration and fungicidal at higher concentration.

**Uses:**

1- It is used for treating Aspergillosis in horses and mycotic mastitis in cattle.

2- In the local treatment of mycotic endometritis in cows or horses, infusions of 400–600 mg Clotrimazole every other day for 12 days has been recommended, using sufficient volume of saline diluent to gently fill the uterus.

3- It may be the drug of choice for yeast mastitis in cows. Intramammary administration of 100–200 mg/ quarter/day of 1% solution or cream, on 1–4 occasions as a single daily dose, has given good clinical results in the treatment of mycotic mastitis in cows.

- **Miconazole:**

- It highly effective against Aspergillosis

- It is used as cream for ring worm.

-It is not absorbed orally.

- It is given by injection for systemic infections

## 3- Organic acids:

- **Benzoic acid** 6% is fungistatic.

**-Salicylic acid** 2-3% is fungistatic or keratolytic

- They are used together for ring worm infections.

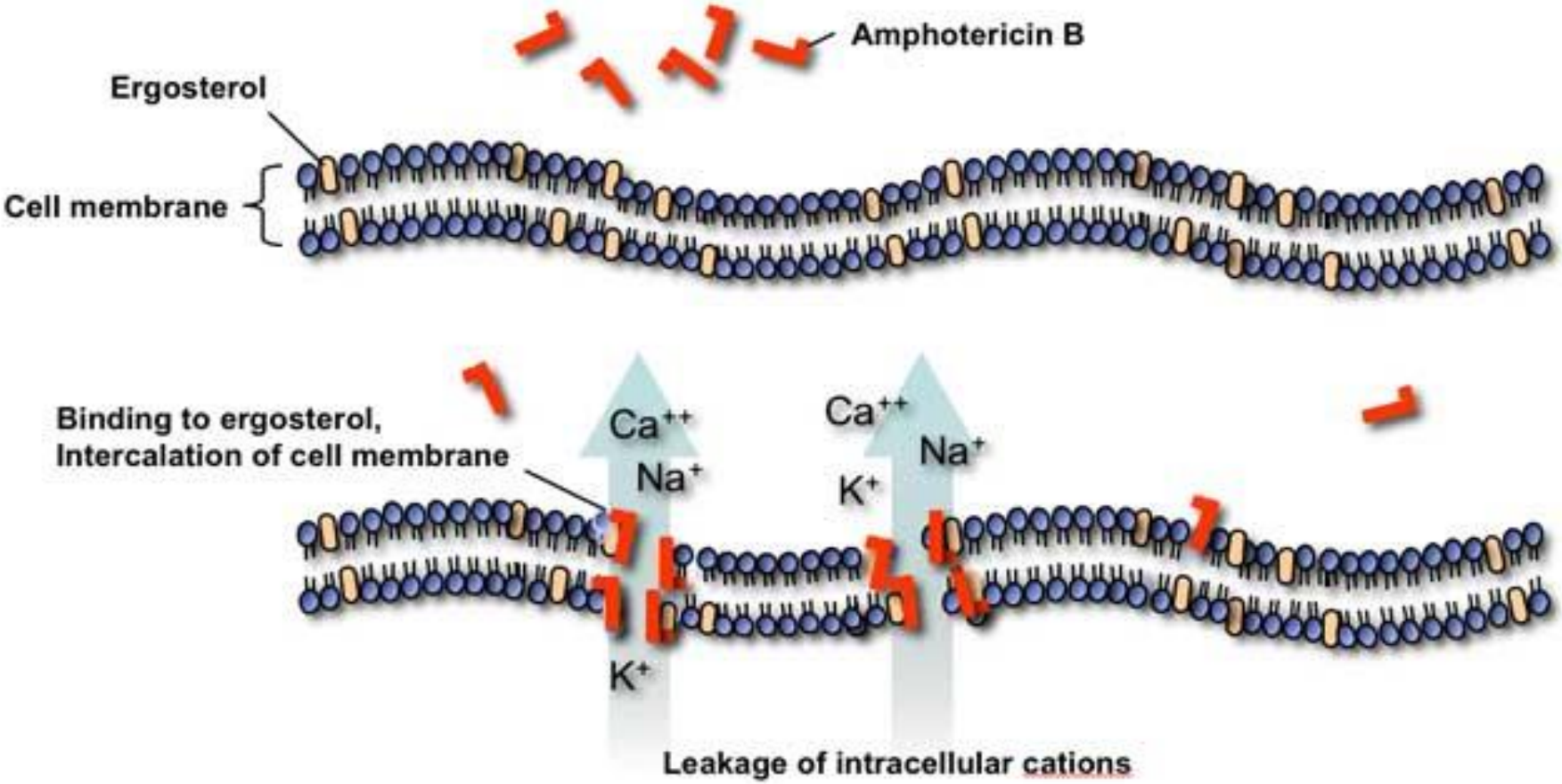
## B- Systemic antifungals:

### Amphotericin B:

- Isolated from *Streptococcus nodosus*
- It is insoluble in water.
- It increases protein synthesis

**Mechanism of action: (**It is fungicidal)

- It binds to ergosterol within the fungal cell membrane resulting in depolarization of the membrane and the formation of pores. The pores permit leakage of intracellular contents.
- It is fungicidal.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Ergosterol
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Leakage of intracellular cations

## Spectrum of activity:

-It is a broad spectrum antifungal

- It is active against most molds and yeasts

## Therapeutic uses:

- It is used for treatment of fungal infections in dogs, cats, horses and birds.

- It is used in combination with flucytosine in treatment of CNS, bone and ocular infections.

## Adverse effects:

-Nephrotoxicosis

## Ketoconazole:

- It is an Imidazole antifungal for systemic use.

## Mechanism of action:

- It acts by inhibiting the synthesis of ergosterol in fungal cytoplasmic membranes by blocking the cytochrome P-450 enzyme

-It is fungicidal.

It inhibits 14-α-sterol demethylase, which is a microsomal CYP450 enzyme.

This enzyme is responsible for conversion of lanosterol to ergosterol, the major sterol of most fungal cell membranes

**Pharmacokinetics:**

- Orally, it needs acidic environment for absorption.

- Only available in oral dosage form.

-Distributes into epidermis, synovial fluid, saliva, and lungs.

- Poor distribution into CSF and eye.

**-Spectrum of activity:**

1- It is effective against most pathogenic fungi responsible for systemic infections (e.g. Blactomyces, Coccidiodes, Cryptococcus, Histoplasma, Microsporum and Trichophyton).

2- It is also effective against Candidiasis (Yeast infections) and Griseofulvin resistant Dermatophytes.

**Uses:**

1- It is used for treatment of systemic mycosis and severe yeast infections in dogs, cats, horses and birds.

2- In treatment of hyperadrenocorticism

## Griseofulvin:

1- It is produced by species of Penicillium (*Penicillium griseofulvum*).

2- It is a very slightly soluble in water.

## Mechanism of action:

- It is a fungistatic antibiotic acts by competition with purins for the synthesis of nucleic acids.

- It causes the loss of fungal cell wall and decreasing hyphal growth

**Pharmacokinetics**:

1-It is administered orally twice per day to dogs and cats and once daily to horse for 4-6 weeks.

2- It is not effective locally.

3- Oral absorption is increased by high fat foods.

4- It is distributed to the keratin precursor cells of the skin, hair shafts and nails.

5- It is metabolised by demethylation and glucuronide conjugation and excreted in the urine.

-**Spectrum of activity:**

1- It is effective against Dermatophytes as *Microsporum sp.* And *Trichophyton sp..*

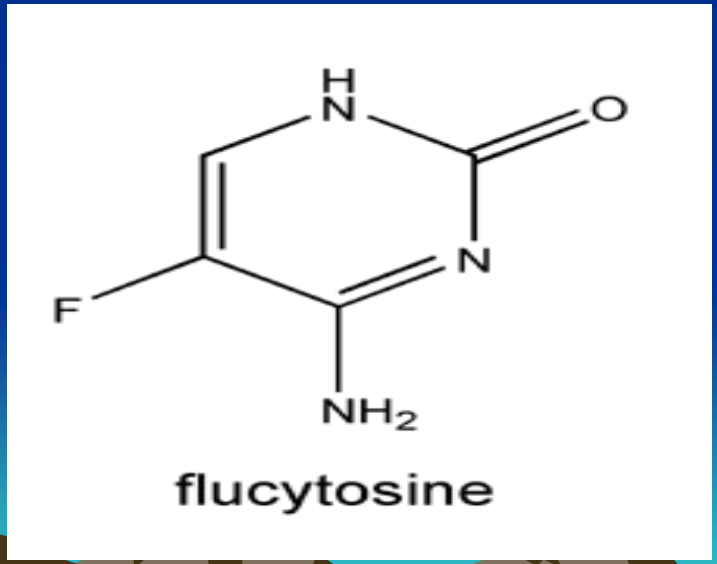
# Flucytosine:

It is a fluorinated pyrimidine antifungal.

# Pharmacokinetics:

1- It is well absorbed well after oral administration.

2- It is widely distributed throughout the body including CNS.



flucytosine

## Mechanism of action:

1- It is converted by cytosine deaminase into 5-fluorouracil which is then converted through a series of steps to 5-fluorouridine triphosphate and incorporated into fungal RNA leading to miscoding

Also, it is converted by a series of steps to 5-fluorodeoxyuridine monophosphate which is a noncompetitive inhibitor of thymidylate synthase, interfering with DNA synthesis

## Spectrum of Activity:

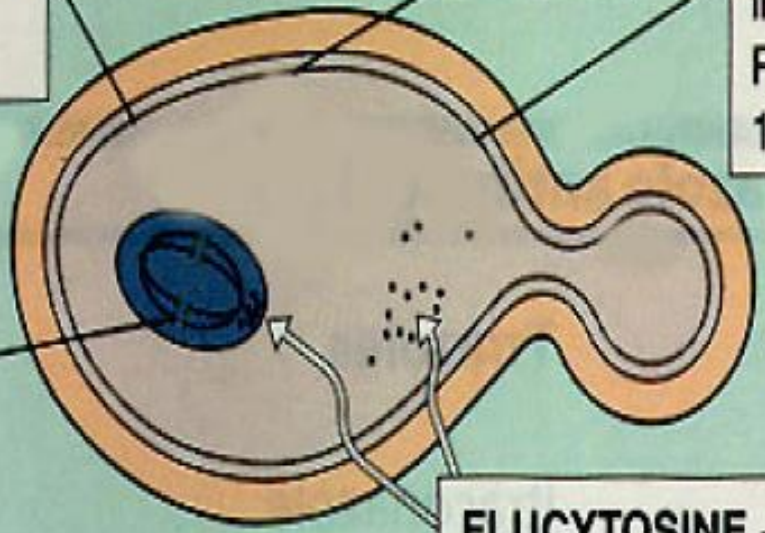
It is active against : *Candida species*, *Cryptococcus species* and *Aspergillus species*

## Uses:

1- It is used alone in treating Aspergillosis and Candidiasis in birds.

2- It is used in combination with Amphotericin B (Synergistic action) in treatment of Cryptococcosis in dogs and cats

# SITES OF ACTION OF ANTIFUNGAL DRUGS



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**ALLYLAMINES**
block ergosterol formation in cell membrane via inhibition of squalene epoxidase

1a

**POLYENES**
bind to and disrupt cell membranes

3

**AZOLES**
block ergosterol formation in cell membrane via inhibition of cytochrome P450 dependent 14 α-demethylase

1 b

**GRISEOFULVIN**
blocks intracellular microtubules

**FLUCYTOSINE** - active uptake via permease blocks DNA/RNA synthesis

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