# ANTIFUNGAL DRUGS

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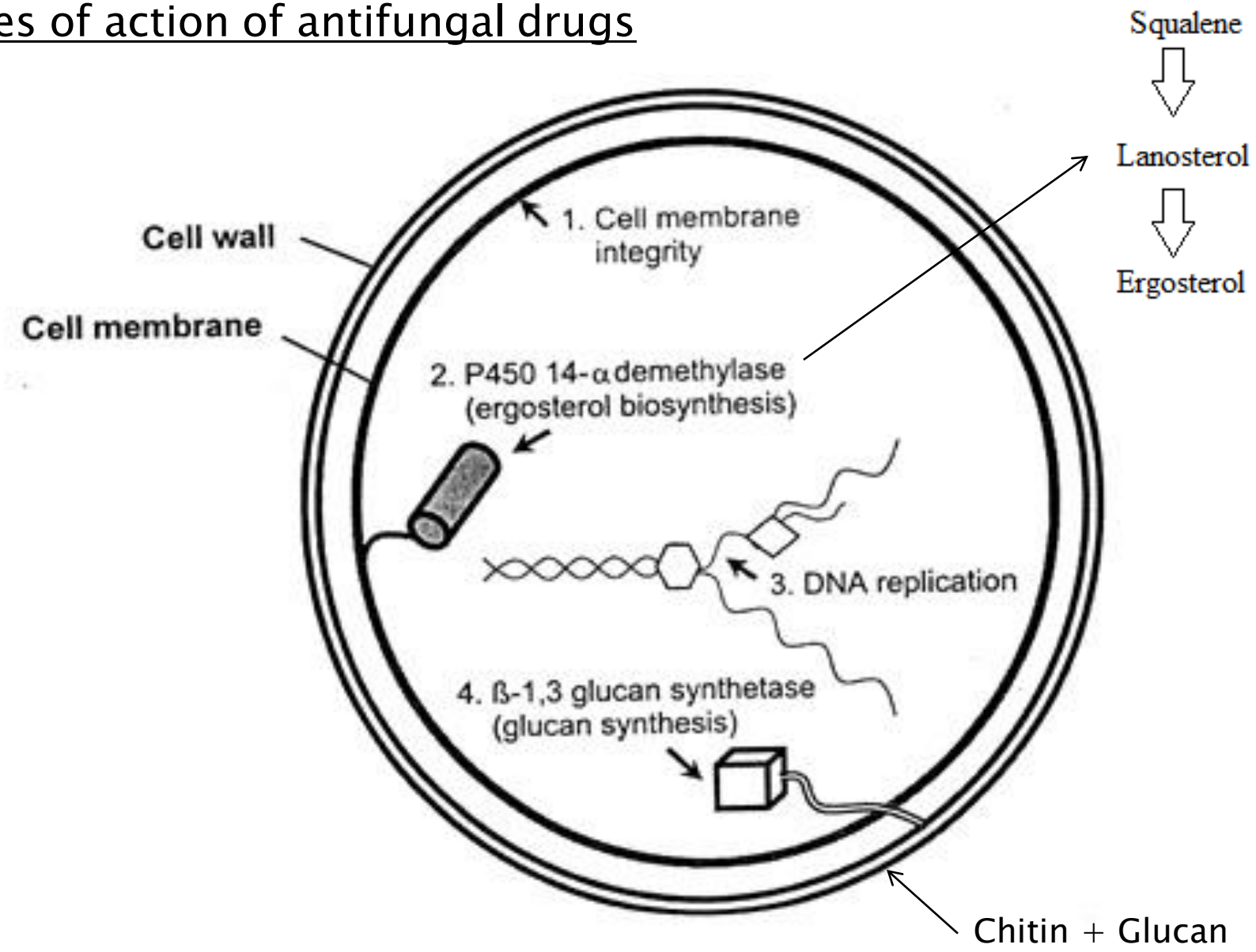
# Definition

- Antifungal drugs are those drugs which inhibit or retard fungal growth.

# Sites of action of antifungal drugs



| SITE OF ACTION | DRUGS |
|---|---|
| *Cell membrane* | |
| Ergosterol binding | Amphotericin B, Natamycin and Nystatin |
| Ergosterole synthesis inhibitors (Squalene epoxidase inhibitor) | Allylamines (Amorolfine, Terbinafine etc.) |
| Ergosterol synthesis inhibitors (lanosterol to ergosterol) | Azoles (Ketoconazole, Miconazole etc.) |
| *Cell wall* | |
| β glucan synthase inhibitor | Echinocandins |
| *Intracelluler* | |
| Pyrimidine analogue | Flucytosine |
| Mitotic inhibitors | Gresiofulvin |
| *Other site* | Benzoic acid , salicylic acid, tolnaftate, castor oil etc. |

# Amphotericin B

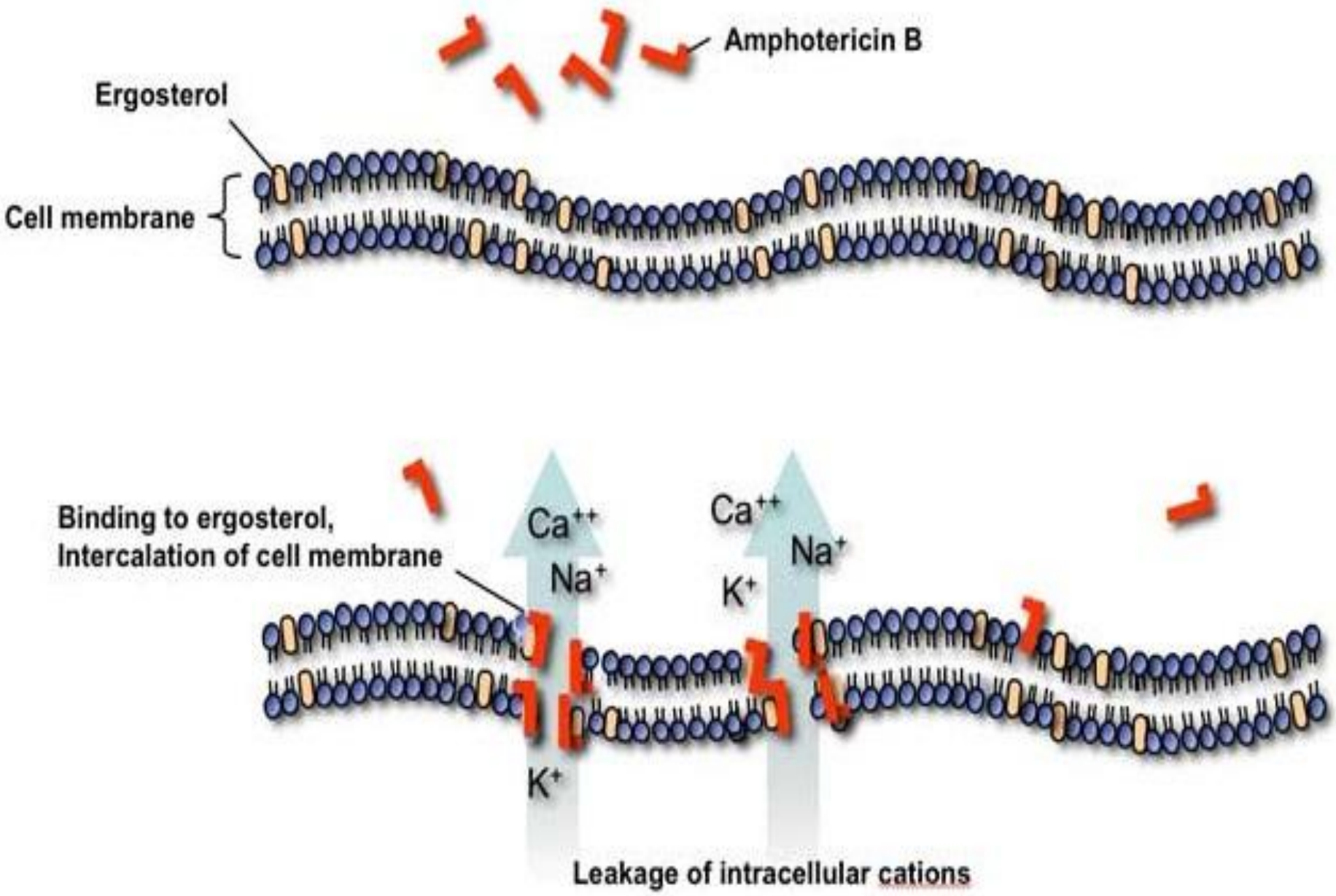
- Source – *Streptomyces nodosus*
- Mechanism of action – Increases permeability of cell membrane by binding to ergosterol

- Antimicrobial spectrum – broad spectrum
- Resistance – when less ergosterol in membrane
- Pharmacokinetics – poorly absorbed from GIT, do not cross BBB
- Adverse effects - Nephrotoxicity
- Drug interaction –

  1. with miconazole antagonistic effect
  2. with flucytosine synergistic effect

- Dose – Dog -0.25 to 0.50 mg/kg, 3 times weekly

  Cat – 0.1 to 0.50 mg/kg, 3 times weekly


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

# Nystatin

- Source – *Streptomyces noursie*
  *Streptomyces aureus*

- Mechanism of action –
  It binds to ergosteol and forms pores in cell membrane

# Natamycin

- Source - *Streptomyces natalensis*

- Mechanism of action –

  Binds to ergosterol and cause leakiness of cell membrane

# Azoles

- Pentameric ring compounds containing at least one other non-carbon atom of either nitrogen, sulfur, or oxygen.

- Inhibit the enzyme that performs demethylation step in the biosynthetic pathway between lanosterol and ergosterol.

- Two types

1. Imidazoles – Ketoconazole, Miconazole, Clotrimazole etc.
2. Triazoles – Fluconazole, Itraconazole, Hexaconazole etc.

# Ketoconazole

- Inhibit steroid synthesis in host
- Absorbed at acidic pH, so antacids will lower the drugs absorption when taken orally.
- Dose –

  Dogs – 5 to 20 mg/kg, 2 times daily

  Cats – 5 to 20 mg/kg, 2 times daily

# Fluconazole

- Triazole drug
- Drug of choice for fungal meningitis because can cross BBB
- Dose –

  Dogs – 5 to 10 mg/kg, 1to 2 times daily

# Terbinafine

- Synthetic allylamine antifungal agent
- Terbinafine inhibits ergosterol synthesis by inhibiting squalene epoxidase, an enzyme that is part of the fungal cell membrane synthesis pathway
- Dose-

  Dog and cat – 3 to 10 mg/kg, once daily

# Amorolfine

- Amorolfine inhibits enzymes, which depletes ergosterol and causes ignosterol to accumulate in the fungal cytoplasmic cell membranes.

# Echinocandins

- Echinocandins are antifungal drugs that inhibit the synthesis of glucan in the cell wall, by noncompetitive inhibition of the enzyme 1,3-β glucan synthase

- It includes capsofungin, micafungin etc.

# Flucytosine

- Mechanism of action

  1. It is converted to 5 furouracil which inhibit thymidylate synthetase enzyme
  2. It inhibits transcription as 5FUTP( 5 flurouracil ribose triphosphate)

- Adverse effects

  Bone marrow depression, convulsion in cat, alopecia in dog
  Not to be given in pregnant animal

- Use

  25 to 50 mg/kg

- Drug interaction

  Flucytosine + Amphotericin B show synergistic effect
  Not combined with immunosuppresent drugs

# Griseofulvin

- Source – *Penicillium griseofulvinum*
- Mechanism of action – inhibit mitosis by interfering spindle fiber formation
- Antimicrobial spectrum
- Resistance – due to reduced drug uptake
- Pharmacokinetics – low water solubility, bind with keratin layer
- Adverse effects – in cat leucopenia, neurotoxicosis and increased hepatic enzyme activity, avoid in pregnant animals
- Drug interaction – not used with phenobarbitone and warfarin, hepatotoxic with ketoconazole

# Benzoic acid & Salicylic acid

- In combination are used as antifungal ointment known as “Whitfield’s ointment”

# Castor oil

- Has  an organic unsaturated fatty acid Undecylenic acid which acts against fungal skin infections.
- Mechanism of action is unknown

# Tolnaftate

- Inhibits ergosterol biosynthesis
- Combined with salicylate because poor penetration

# Iodides

- It is the first antifungal agent
- Mechanism of action – not known, may cause enhanced immune response and leading to fungus removal

# Lufenuron

- Mainly used in flea treatment because inhibit chitin synthesis in larval forms.
- Due to ability to inhibit chitin formation used against fungal infections

# Propionic acid

- Topical antifungal agent
- Used as 0.1 to 1% solution

# Some other antifungal drugs

- Gentian violet
- Sulphur
- Copper sulfate
- Cliquinole
- Dichlorophen
- Ciclopirox

# THANK YOU