# Antifungal drugs

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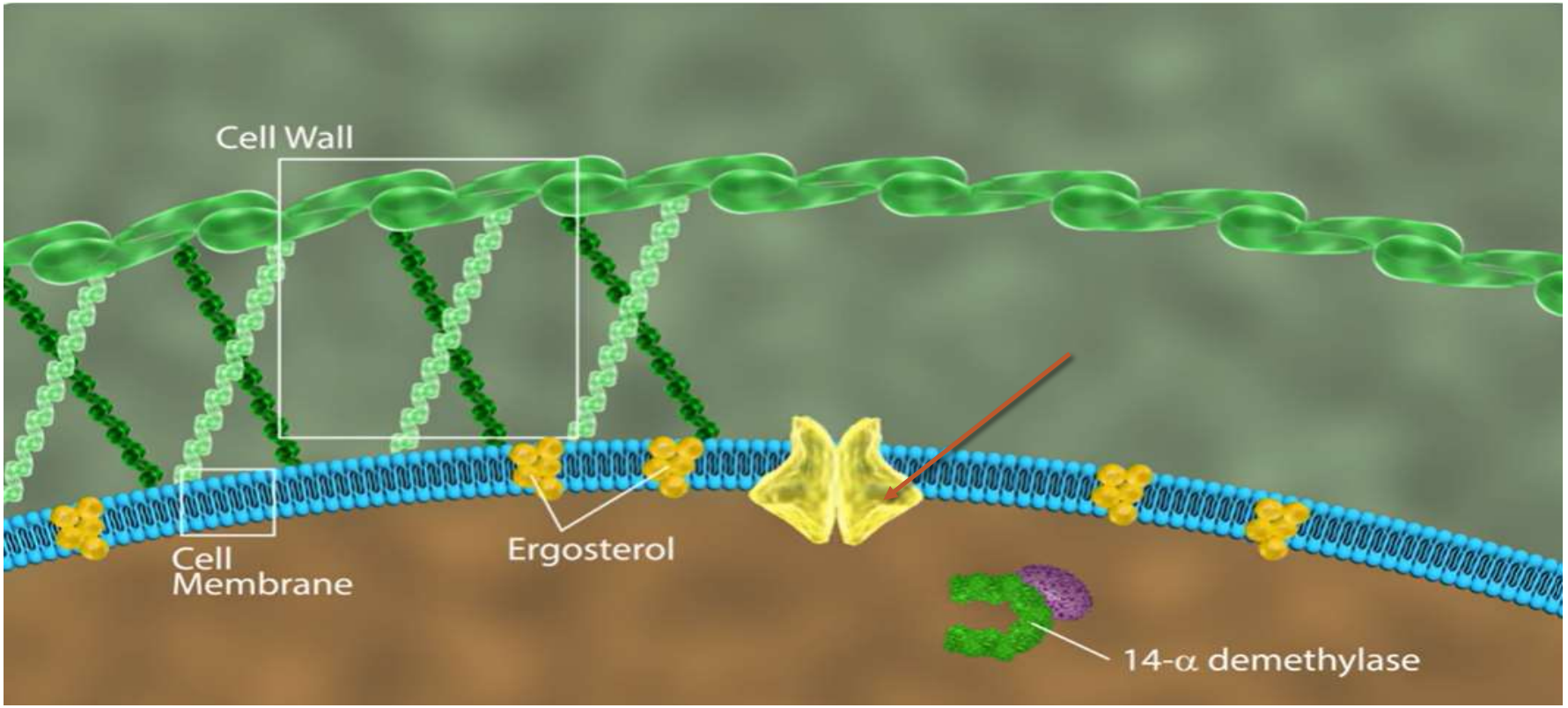
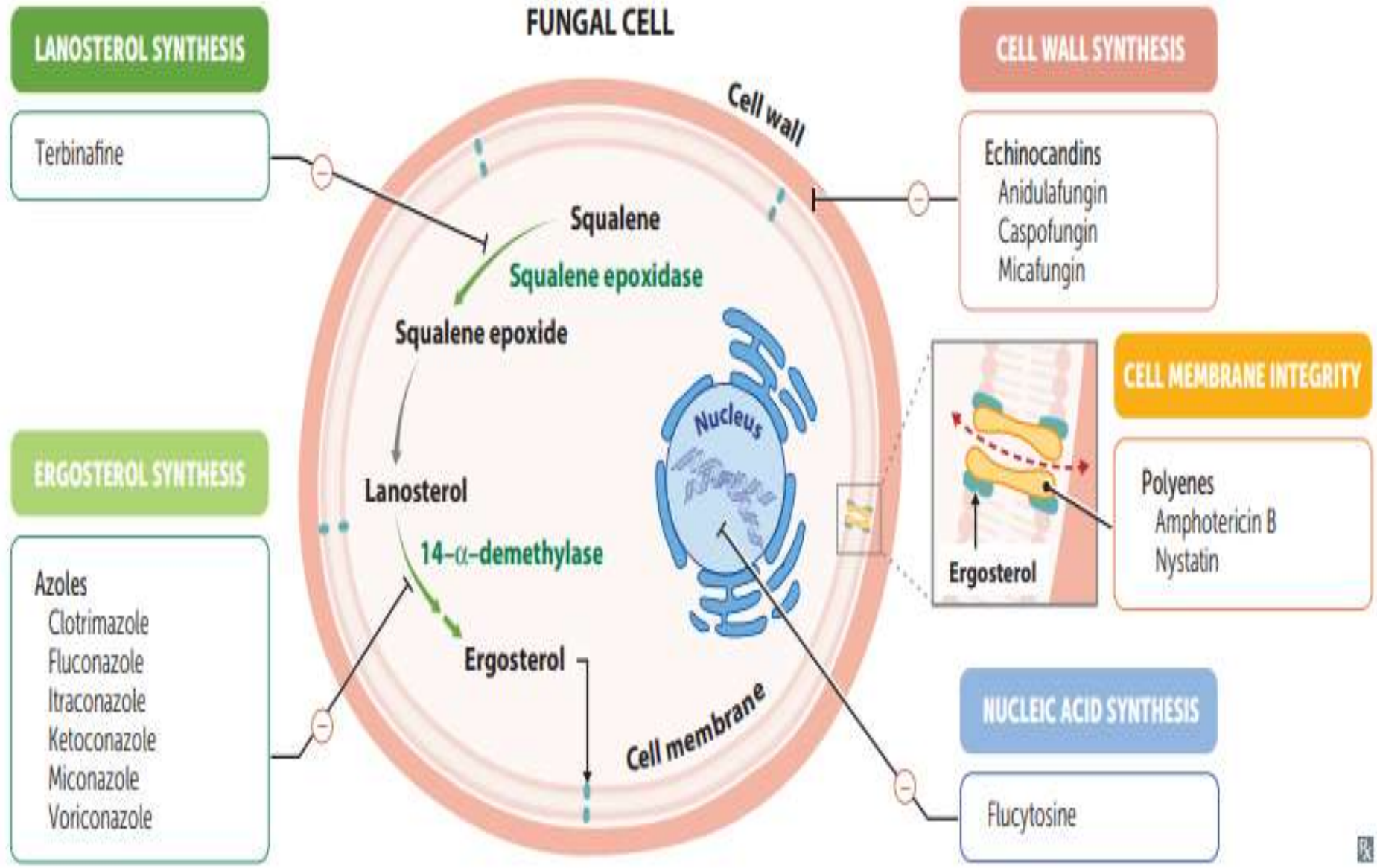
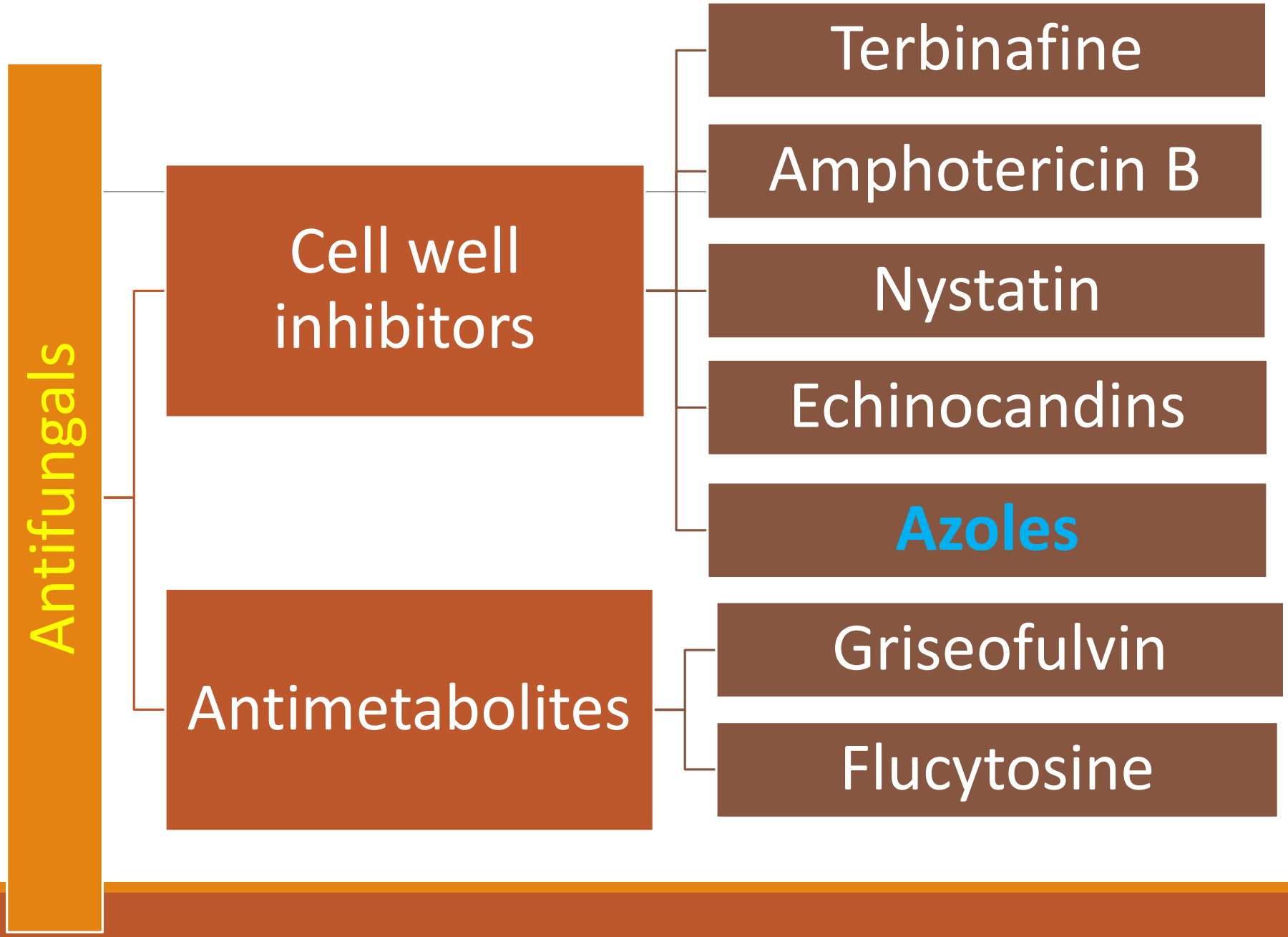
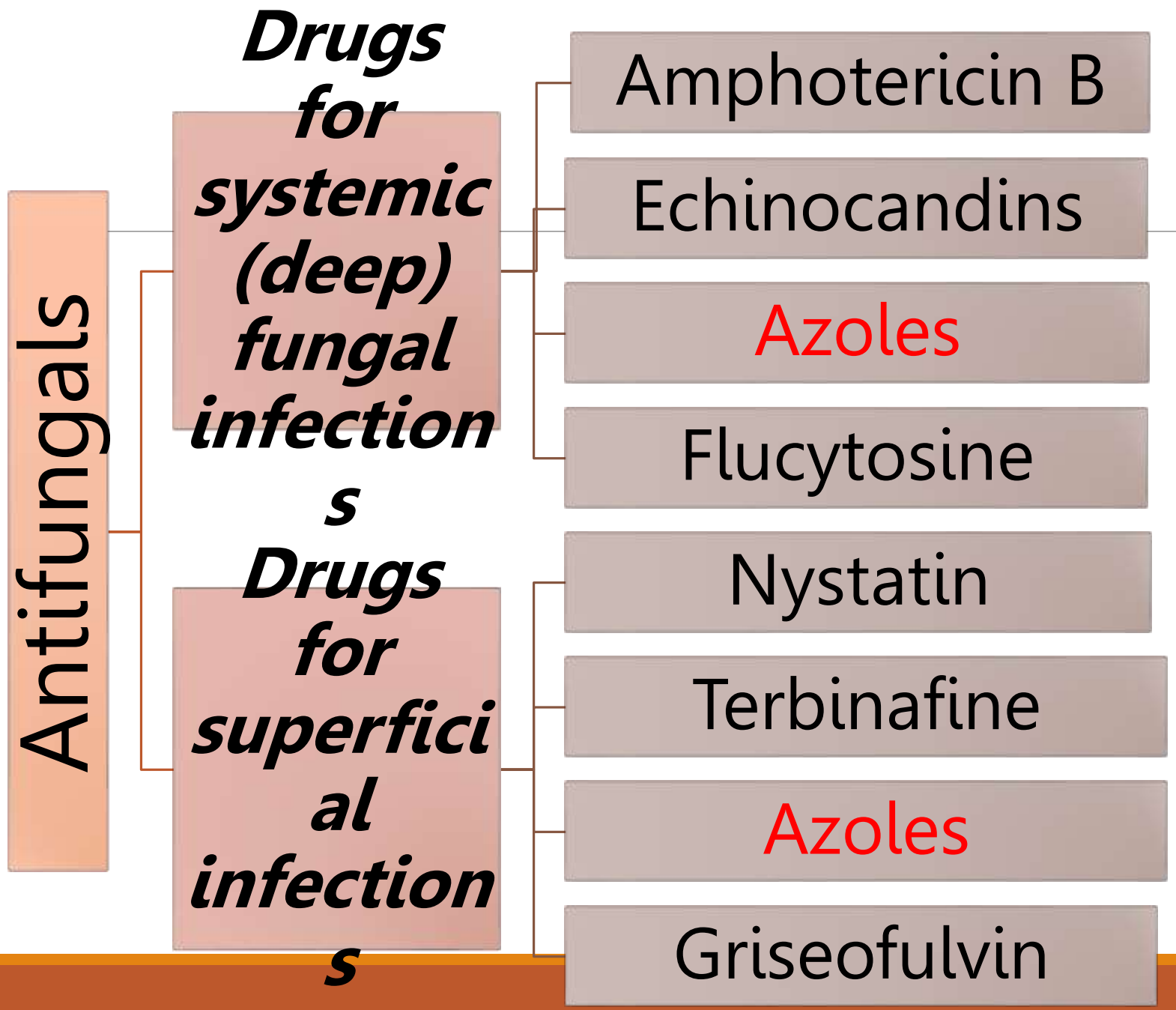
# FUNGAL CELL WALL STRUCTURE



# Antifungal therapy




Antifungals
Cell well inhibitors
Terbinafine
Amphotericin B
Nystatin
Echinocandins
Azoles
Antimetabolites
Griseofulvin
Flucytosine


Antifungals
Drugs for systemic (deep) fungal infections
Drugs for superficial infections
Amphotericin B
Echinocandins
Azoles
Flucytosine
Nystatin
Terbinafine
Azoles
Griseofulvin

# Terbinefine

**pk**:

- *Oral active, Bioavailability 40% due to 1st pass metabolism*
- *99% bound to plasma protein*
- *Deposited in nails, skins, and fats, milk*
- *T1/2=200-400h*
- *Extensive metabolism in liver*
- *Excreted in urine*

**Mechanism**: ***fungicidal***

Inhibition of squalene epoxidase enzyme which is essential for ergosterol synthesis of cell membrane.

**Indications:**

Systemic (oral) & topical for dermatophytcs (more effective than griseofulvin). Duration of treatment up to 3 months.

**Side effects**:

GIT and taste disturbances, hepatotoxicity, headache, visual disturbance.

# Advantages over Azoles:

1. Squalene epoxidase enzyme is not present in human (more selective toxicity).

2. No inhibition of cytochrome $P_{450}$ (no serious adverse effect of azoles).

But affected by enzymes inducers and inhibitors

# Azoles

**Mechanism of action:** **fungicidal**

inhibit ergosterol synthesis of cell membrane by inhibiting fungal cytochrome p450 ( 14 α demethylase) leading to membrane dysfunction.

**Members :**

**1- Ketoconazole**

**2- Itraconazole**

**3- Fluconazole**

4- **Posaconazole**

# Ketoconazole:

1st oral broad spectrum antifungal.

Pk:

Oral and required acidic ph to be absorbed

Extensive bound to plasma protein

Extensive metabolism in liver

**It is used for:**

- Deep fungal infections (mild - non meningeal). 2nd line to amphotericin
- Candida infection.
- Dermatophyles resistant to grisofulvin & terbinafine (oral and topical).

## Avoid combination with:

- Antacids or $H_2$ blockers → decrease gastric acidity → decrease ketoconazole absorption.
- Amphotericin B: ketoconazole → decrease amphotericin effect by decreasing ergosterol

## Adverse effects:

1. Nausea - vomiting - rash (common).
2. Hepatotoxic (serious).
3. **Inhibition of human cytochromeP450**
4. **Enzyme inhibitor**

## Inhibition of human cytochrome P450 leading to inhibition of

### Steroid synthesis which depends on cytochrome P450:

- Corticosteroids → adrenal suppression (used in Cushing's disease).
- Testesterone → gynecomastia & impotence (used in cancer prostate).
- Female sex hormones → menstrual irregularities & infertility

### Metabolism of drugs → drug interactions:

- Increased level of astemizole & terfenadine → arrhythmia.
- Increased level of oral anticoagulants & antiepileptics.

# Itraconazole and fluconazole

- These drugs are azoles that are more specific to fungal cylochrome $P_{450}$ than to human cytochme $P_{450}$ compared to ketoconazole.
- Less toxic (less effect on human cytochrome $P_{450}$): less hepatotoxic, less adrenal suppression & less drug interactions.
- More effective.

# Fluconazole:

**Drug of choice in esophageal and oropharyngeal candidiasis**.

- Drug of choice in treatment and secondary prophylaxis against cryptococcal meningitis.
- Equivalent to amphotericin B in systemic candidiasis

# *Posaconazole*

- The broadest-spectrum azole.
- The only azole with activity against mucormycosis.
- It is used for prophylaxis of fungal infections during cancer chemotherapy.
- Inhibitor of CYP3A4 → increasing the levels of cyclosporine and tacrolimus

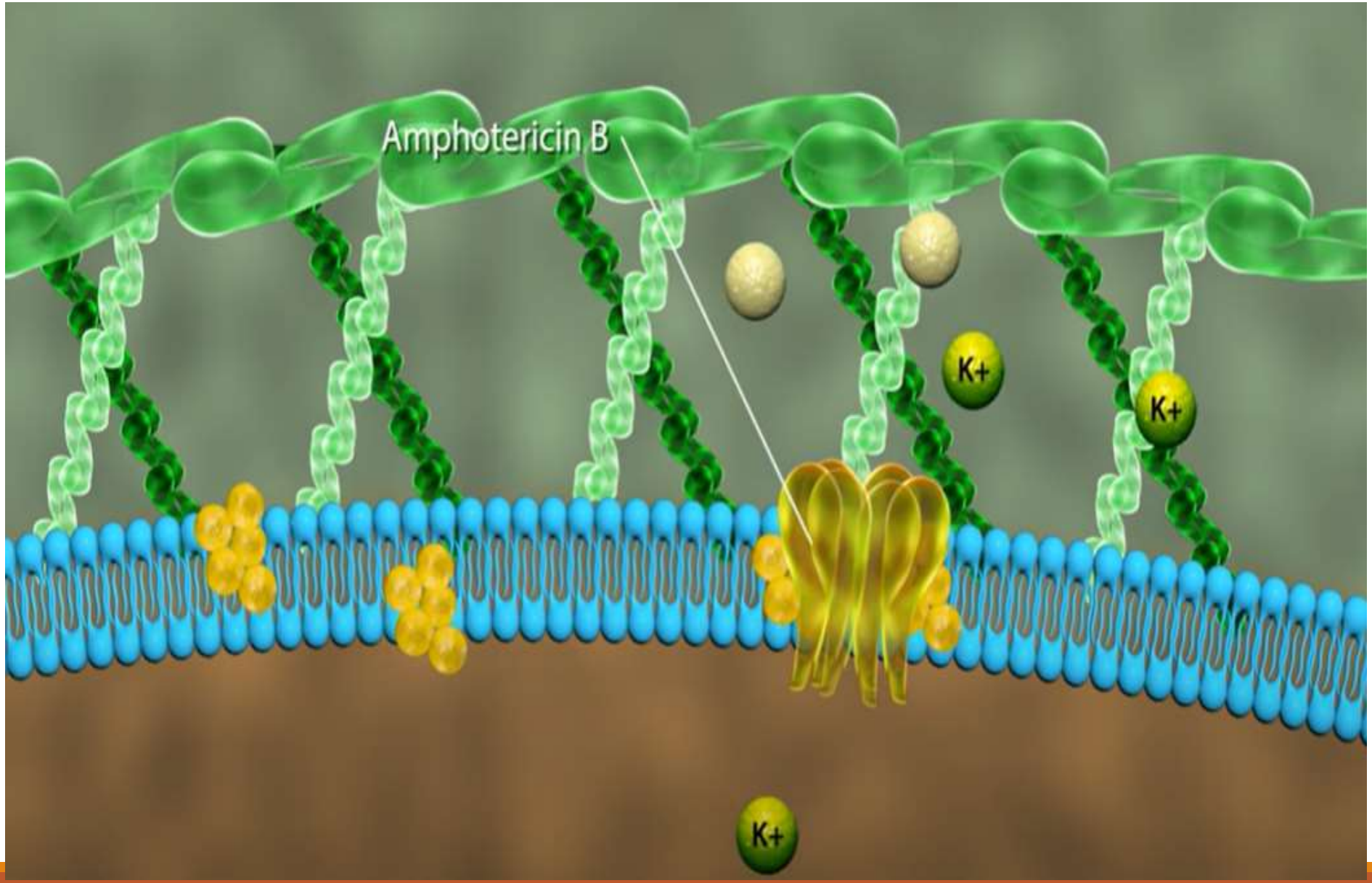
# Amphotericin B

**Mechanism of action:** **fungicidal**

- Binds to ergosterol of cell membrane → formation of artificial pores → leakage of important cell constituents' → cell death.

**Indications:** deep infections **especially**:

- Severe life threatening (I.V - not absorbed orally).
- Meningitis (intrathecal- does not reach CSF after I.V.I).


Amphotericin B
K+
K+
K+

## Side effects & toxicity:

- **Infusion related:** Fever, rigors, vomiting, hypotension & shock after I.V infusion.

  **Can be avoided by**: Slow infusion rate and pretreatment with antihistamines, antipyretics.

- **Dose-related:** nephrotoxicity. **Can be decreased by:** dose reduction.

- **Convulsion**.

# Nystatin

**Mechanism:**

Binds to ergosterol of fungal cell membrane → formation of artificial pores—» damage of membrane → leakage of important cell constituents → cell death.

# **Indications:** (too toxic for systemic use).

***Used locally in:***

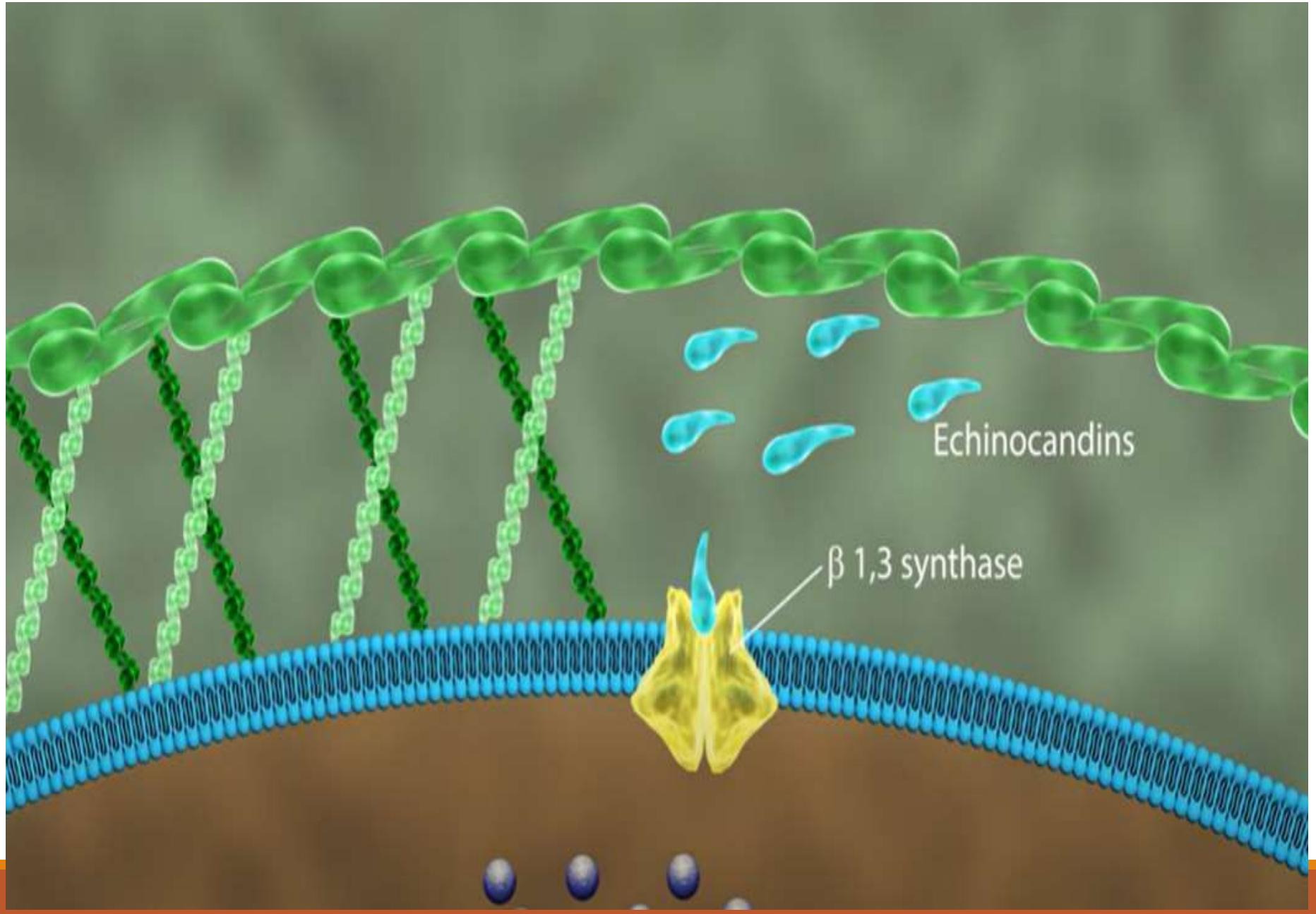
1. Oropharyngeal and Gl Candida: oral (not absorbed).
2. Cutaneous Candida: topical (non irritant- rarely causes allergy).
3. Vaginal Candida: It is given both topically and orally because quite often vaginal Candida is associated with gastrointestinal Candida which acts as a source of reinfection of vagina.

# Echinocandins

## Caspofungin – Micafungin

**Mechanism:**

Inhibits synthesis of a glucose polymer ( glycane synthase) that is necessary for maintaining structure of fungal cell wall → loss of cell wall integrity → lysis & death.


Echinocandins
β 1,3 synthase

## Uses: (IV)

**Caspofungin**: candidiasis & invasive aspergillosis refractory to amphotrericin.

**Micafungin**: mucocutaneous candidiasis and for prophylaxis of *Candida* infections in bone marrow transplant patients

## Adverse Effects:

***Infusion-related:*** GIT upset, headache, fever & flushing (histamine release).

# Flucytosine

**Mechanism of action:**

- Cytotoxic, transformed to 5-flurouracil (5-FU) → inhibits nucleic acid synthesis.
- Selective toxicity occurs because mammalian cells cannot transform flucytosine into 5-FU.
- ***Indications:***

*Given orally with amphotericin or azoles in Cryptococcal infections.*

## Adverse effects:

1. Bone marrow depression (reversible).
2. Hair loss.
3. Hepatotoxic.

## Advantages of combination of flucytosine with amphotericin B:

1. Decrease resistance to amphotericin B.
2. Decrease amphotericin nephrotoxicity (lower doses of amphotericin are used).

# Griseofulvin

**Mechanism: *Fungistatic***

Concentrated in newly formed keratin (e.g nails) preventing its infection by:

Interfering with microtubular function → interfere with mitosis.

Inhibiting nucleic acid synthesis.

**Indications:** not active topically, duration of treatment 6-12 months

- Dermatophyte infections (given orally: decreased absorption by high fat diet).
- Largely replaced by terbinafine & azoles

## Adverse effects :

1. Nausea-vomiting.
2. Headache - mental confusion.
3. Hepatotoxic.
4. Enzyme inducer → decrease warfarin level.
5. Teratogenic , Carcinogenic

# *Systemic therapy is used in:*

1- Resistance to topical therapy.

2- Wide or inaccessible areas.

3- Severe infections.

4- Low immunity of patient.

N.B: Superficial fungal infections are treated first with topical agents

# THANK YOU