Charting New Horizons in Education

Antifungal drugs

19

pharmacology

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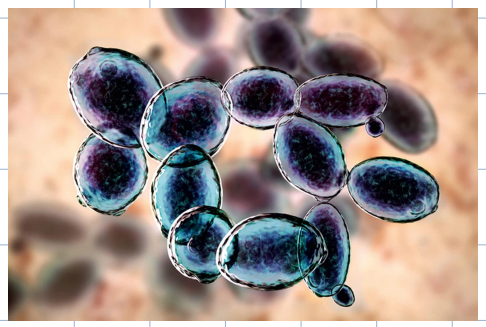
Fungi

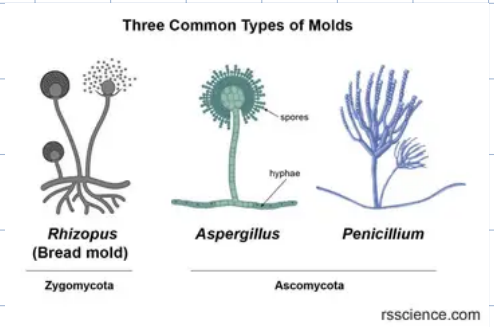
yeasts

* Unicellular
* Asexuall (budding, binary fission)
- Candida albicans
- Cryptococcus neoformans (meningitis)



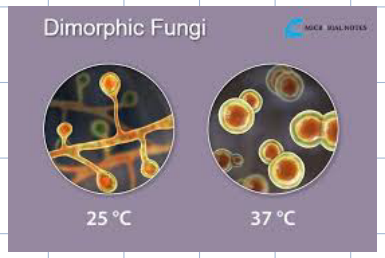
Molds

* Multicellular
* Asexual, sexual
- Aspergillus

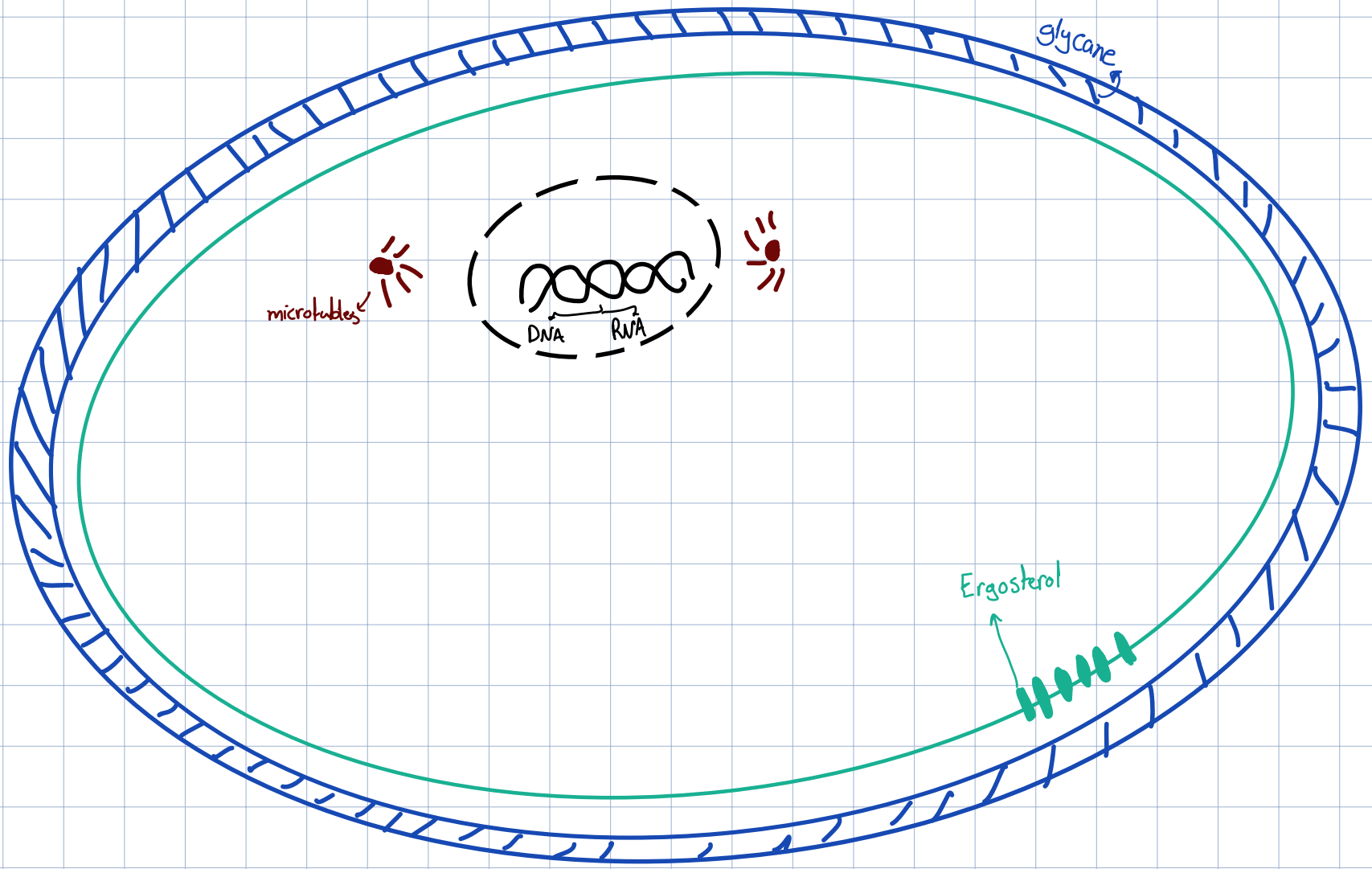


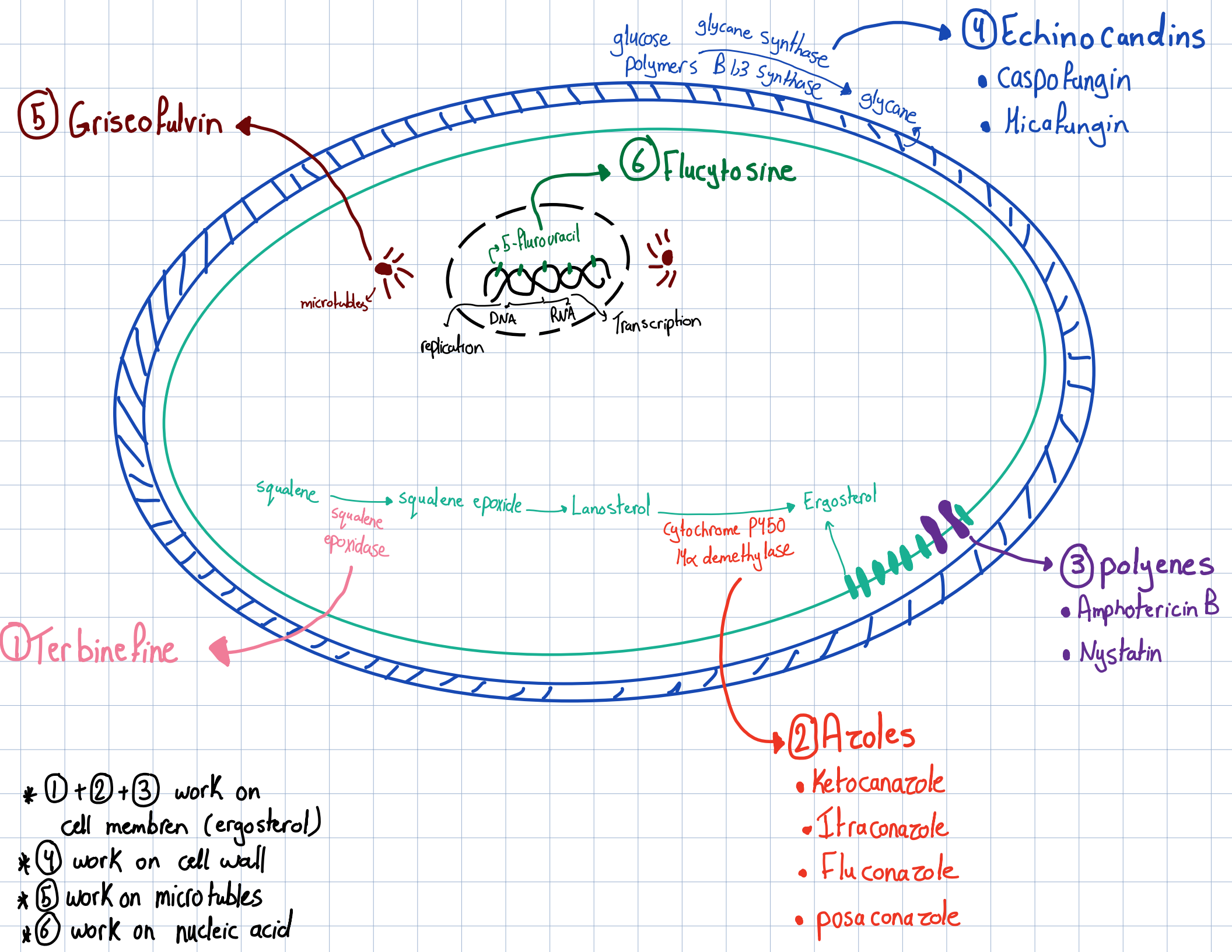
Dimorphic Fungi

* Exist in two forms:-
  yeast at (37°C)
  Mold at (25°C)
- Histoplasma capsulatum

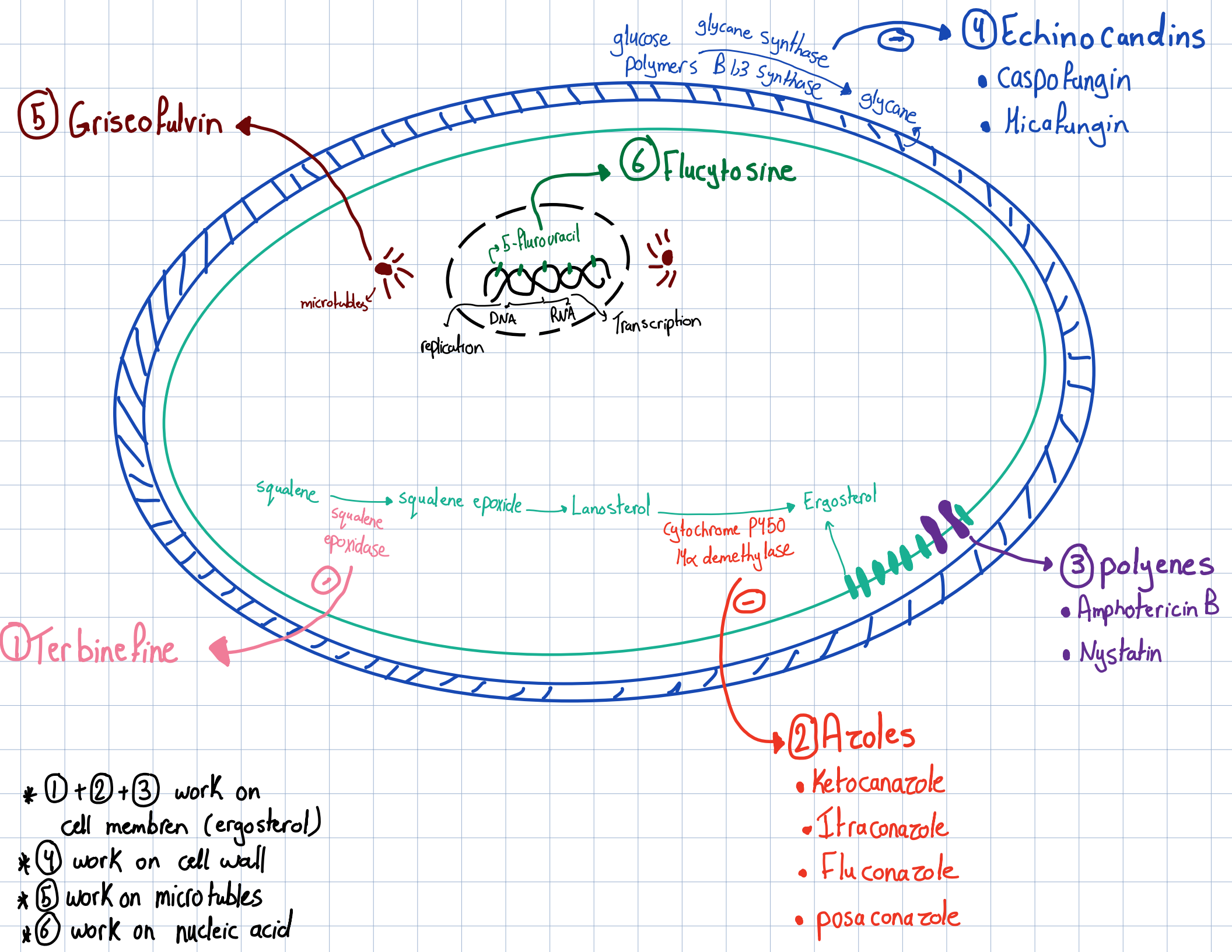


* Dermatophytes:- Fungi that infect Keratinized tissues (skin, hair, nails)


glycane
microtubles
DNA
RNA
Ergosterol



* ① + ② + ③ work on cell membren (ergosterol)
* ④ work on cell wall
* ⑤ work on microtubles
* ⑥ work on nucleic acid



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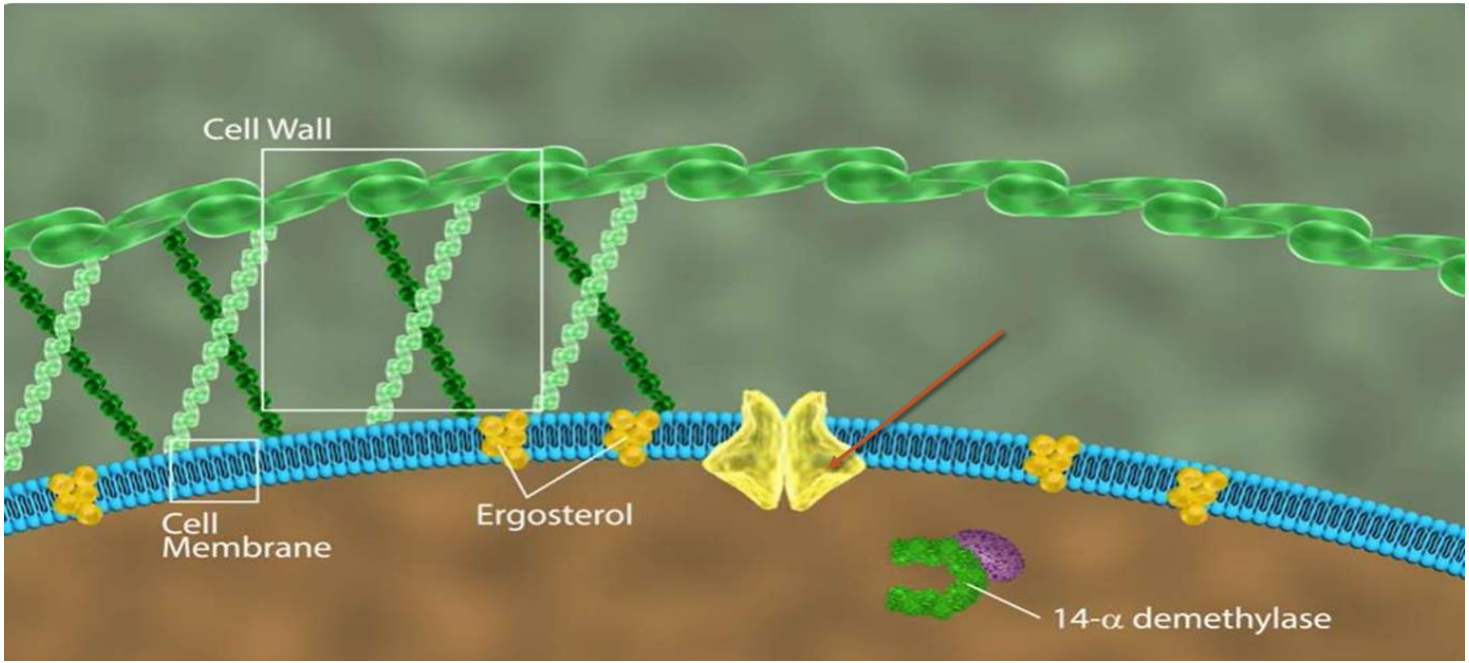
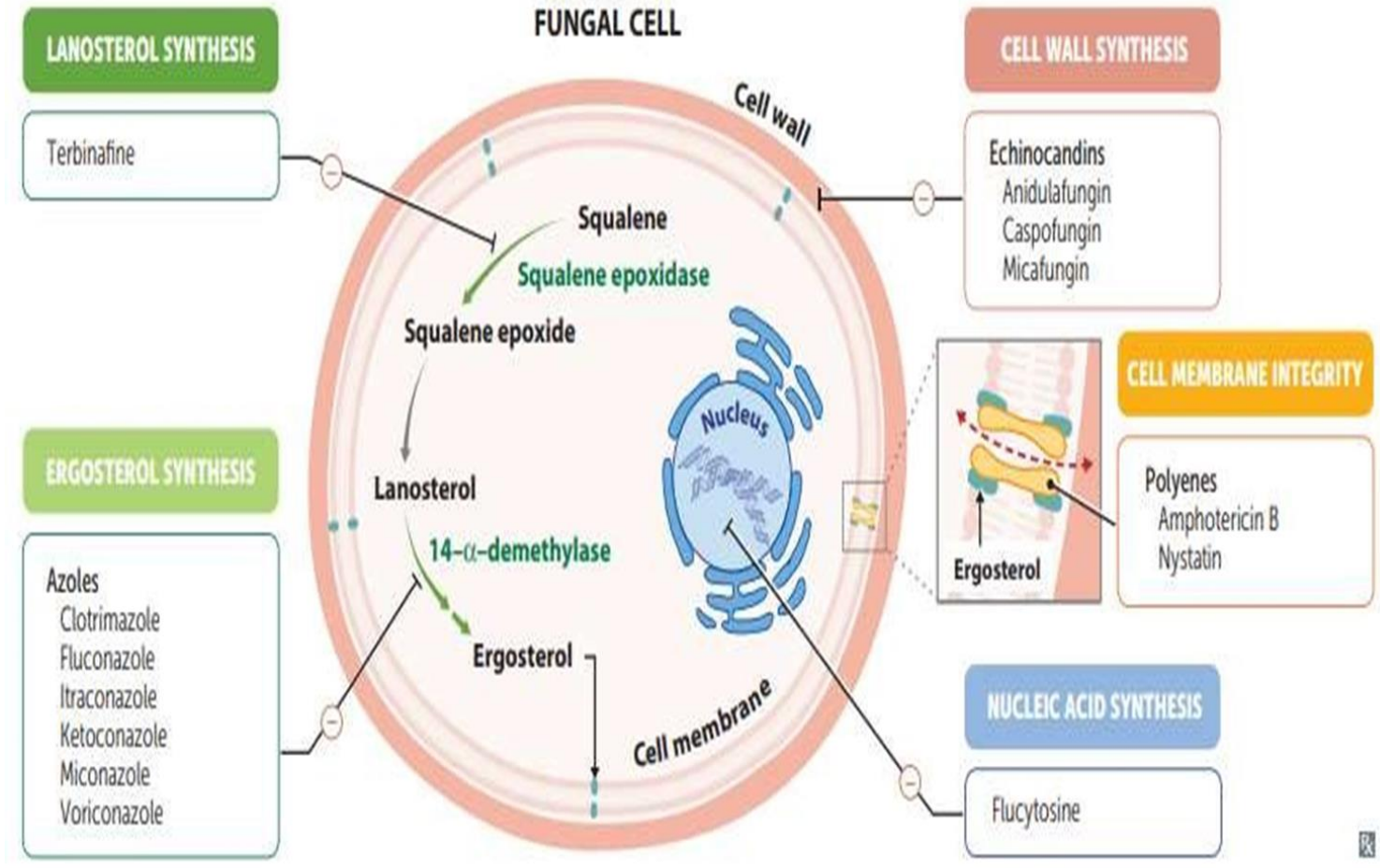
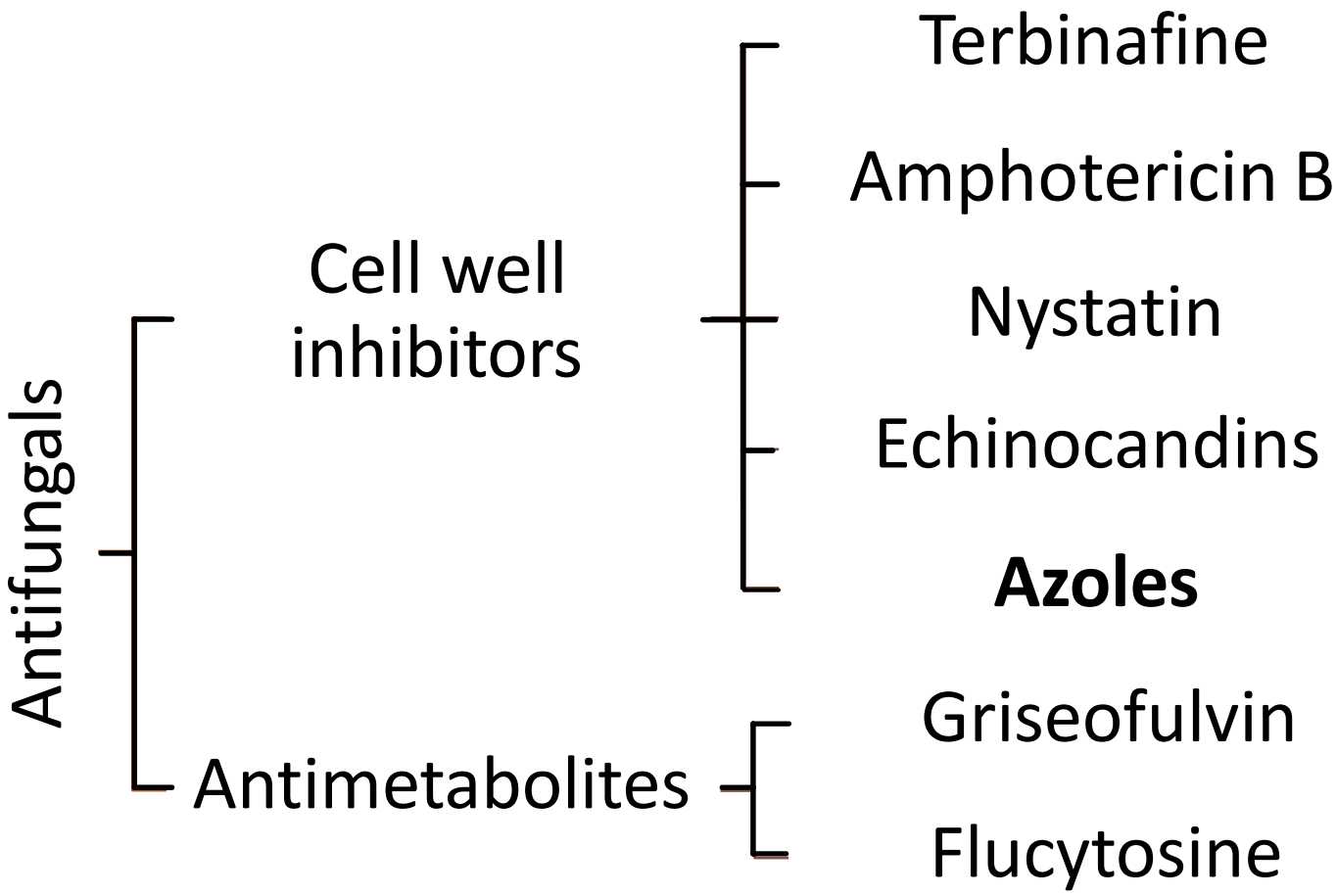
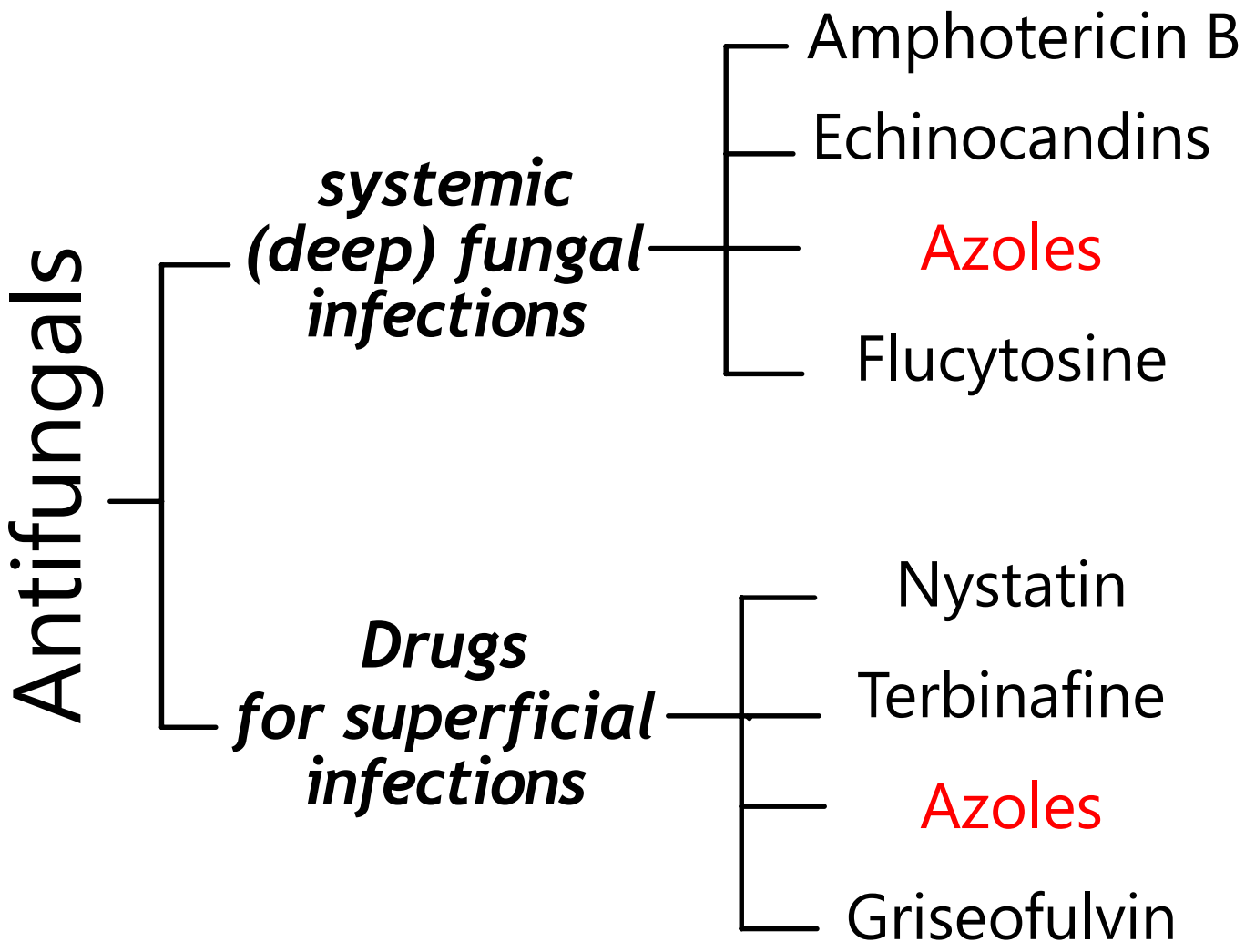
FUNGAL CELL WALL STRUCTURE



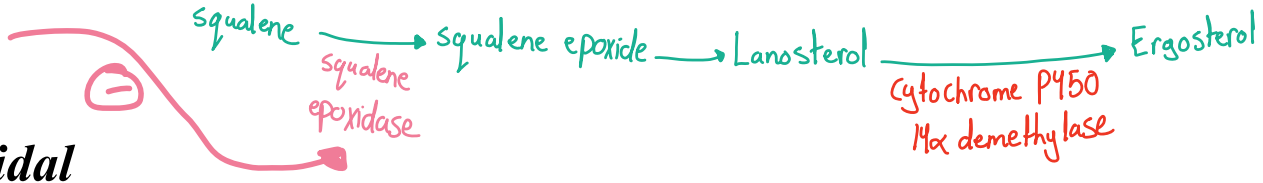
Antifungal therapy




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


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

Terbinefine



Mechanism: ***fungicidal***

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

Indications:

Systemic (oral) & topical form dermatophytcs (more effective than griseofulvin).

Duration of treatment up to 3 months.

Terbinefine

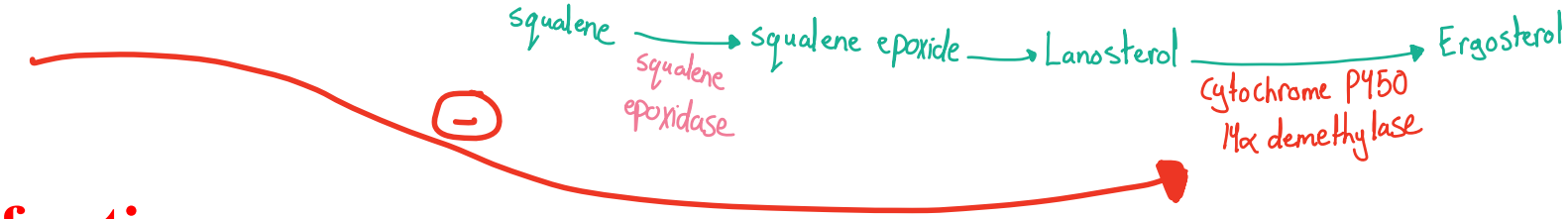
pharmacokinetics:

- Oral active, Bioavailability 40% due to 1st pass metabolism
- 99% bound to plasma protein
- Deposited in nails, skins, and fats, milk (not given in lactating women)
- T1/2=200-400h
- Extensive metabolism in liver
- Excreted in urine

Side effects:

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

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**

Azoles

1.Ketoconazole:

pharmacokinetics:

- 1st oral broad spectrum antifungal.
- 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).

Azoles

1.Ketoconazole:

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:

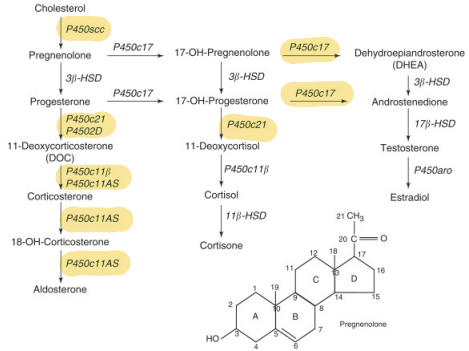
1. Nausea - vomiting - rash (common).
2. Hepatotoxic (serious).
3. **Inhibition of human cytochromeP450**
4. **Enzyme inhibitor**

Azoles

1.Ketoconazole:

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.

Advantages of Terbinefine 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

2.Itraconazole and 3.fluconazole

- These drugs are azoles that are more specific to fungal cytochrome P450 than to human cytochrome P450 compared to ketoconazole.
- Less toxic (less effect on human cytochrome P450): less hepatotoxic, less adrenal suppression & less drug interactions.
- More effective.

Azoles

3.Fluconazole:

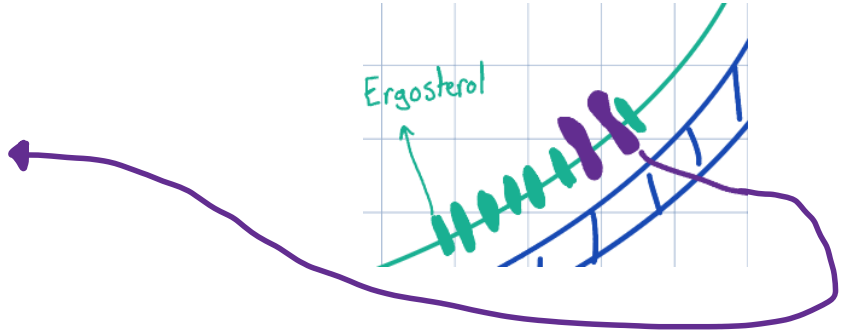
- Drug of choice in esophageal and oropharyngeal candidiasis.
- Drug of choice in treatment and secondary prophylaxis against cryptococcal meningitis.
- Equivalent to amphotericin B in systemic candidiasis

Azoles

4.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

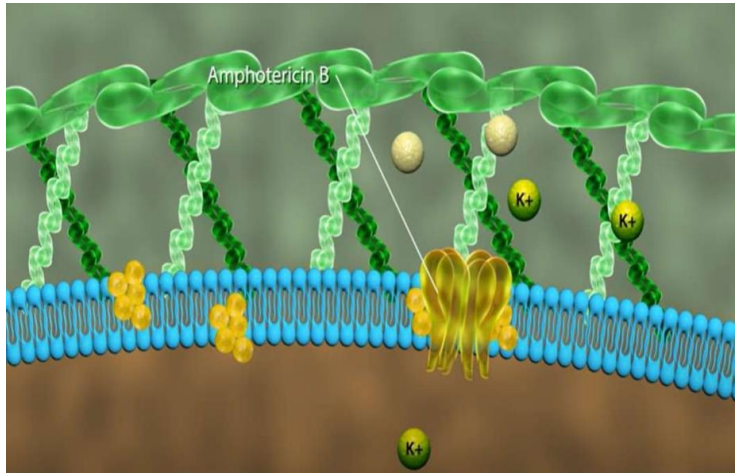


Mechanism of action: **fungicidal**

- 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).

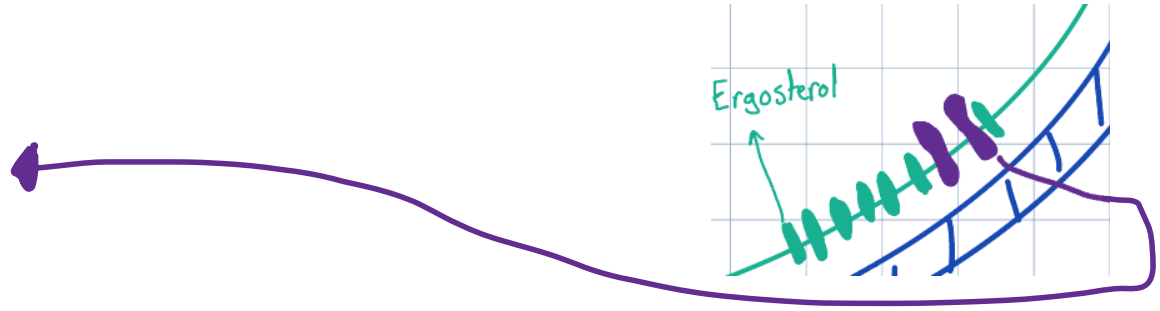


Amphotericin B

Side effects & toxicity:

- **Infusion related:** Fever, rigors, vomiting ,hypotension & shock after I.V infusion. **Can be avoided by**: Slow infusion rate and pre treatment 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.

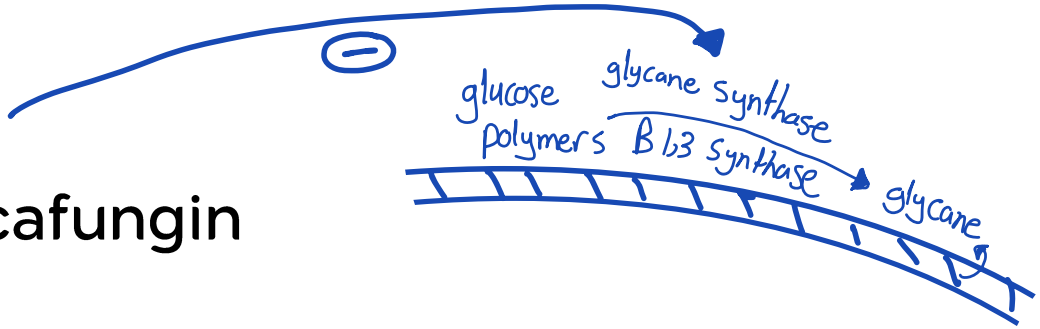
Indications:

(too toxic for systemic use).

Used locally in:

- **Oropharyngeal and GI Candida:** oral (not absorbed).
- **Cutaneous Candida:** topical (non irritant- rarely causes allergy).
- **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.

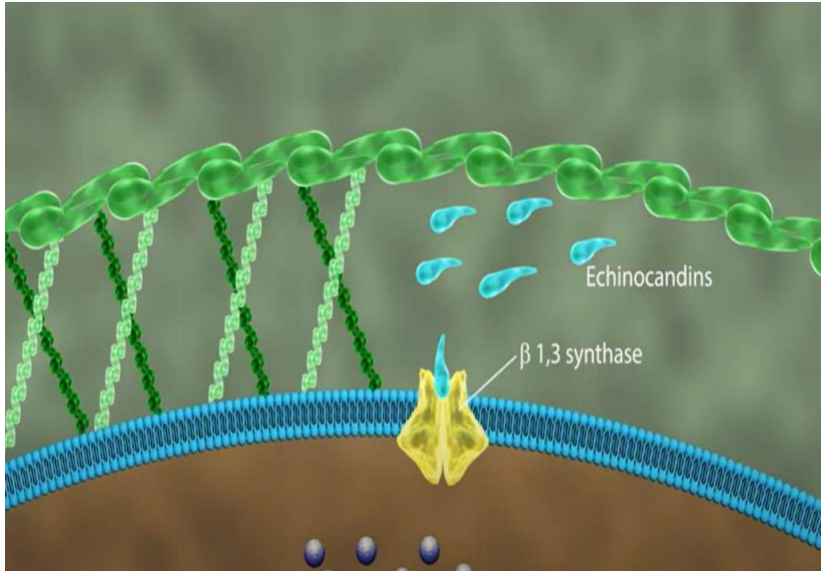
Echinocandins



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

Caspofungin – Micafungin

Uses: (IV)

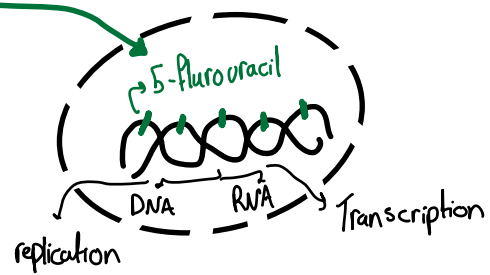
Caspofungin: candidiasis & invasive aspergillosis refractory to amphotrericin.

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



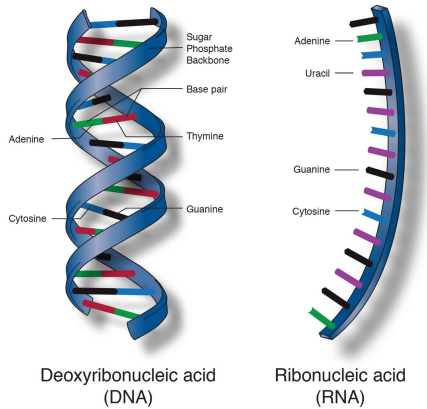
Mechanism of action:

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.



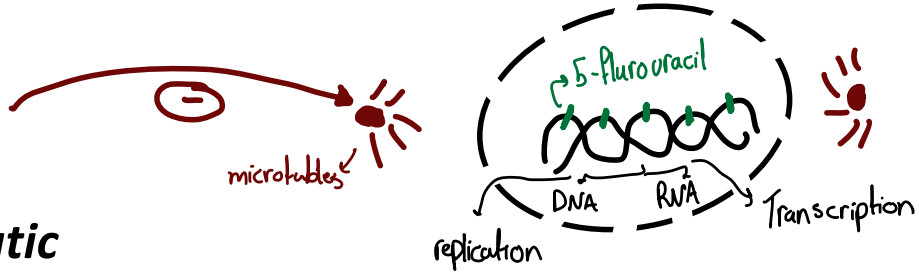
Adverse effects:

- Bone marrow depression (reversible).
- Hair loss.
- Hepatotoxic.

Advantages of combination of flucytosine with amphotericin B: (synergism)

- Decrease resistance to amphotericin B.
- 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

Terbinefine is used more than griseofulvin because it is fungicidal , and its duration of treatment is 3 months .

Griseofulvin

Adverse effects :

- Nausea-vomiting.
- Headache - mental confusion.
- Hepatotoxic.
- Enzyme inducer → decrease warfarin level.
- Teratogenic , Carcinogenic

Systemic therapy is used in:

- Resistance to topical therapy.
- Wide or inaccessible areas.
- Severe infections.
- Low immunity of patient.

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

«Wherever the art of medicine is loved,
there is also a love of humanity.»

- Hippocrates-