Athar Batch

Pharmacology

Lecture: 35

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النادي الطبي

Fungal Cell Wall Synthesis Inhibitors

more rigid than the bacterial cell wall

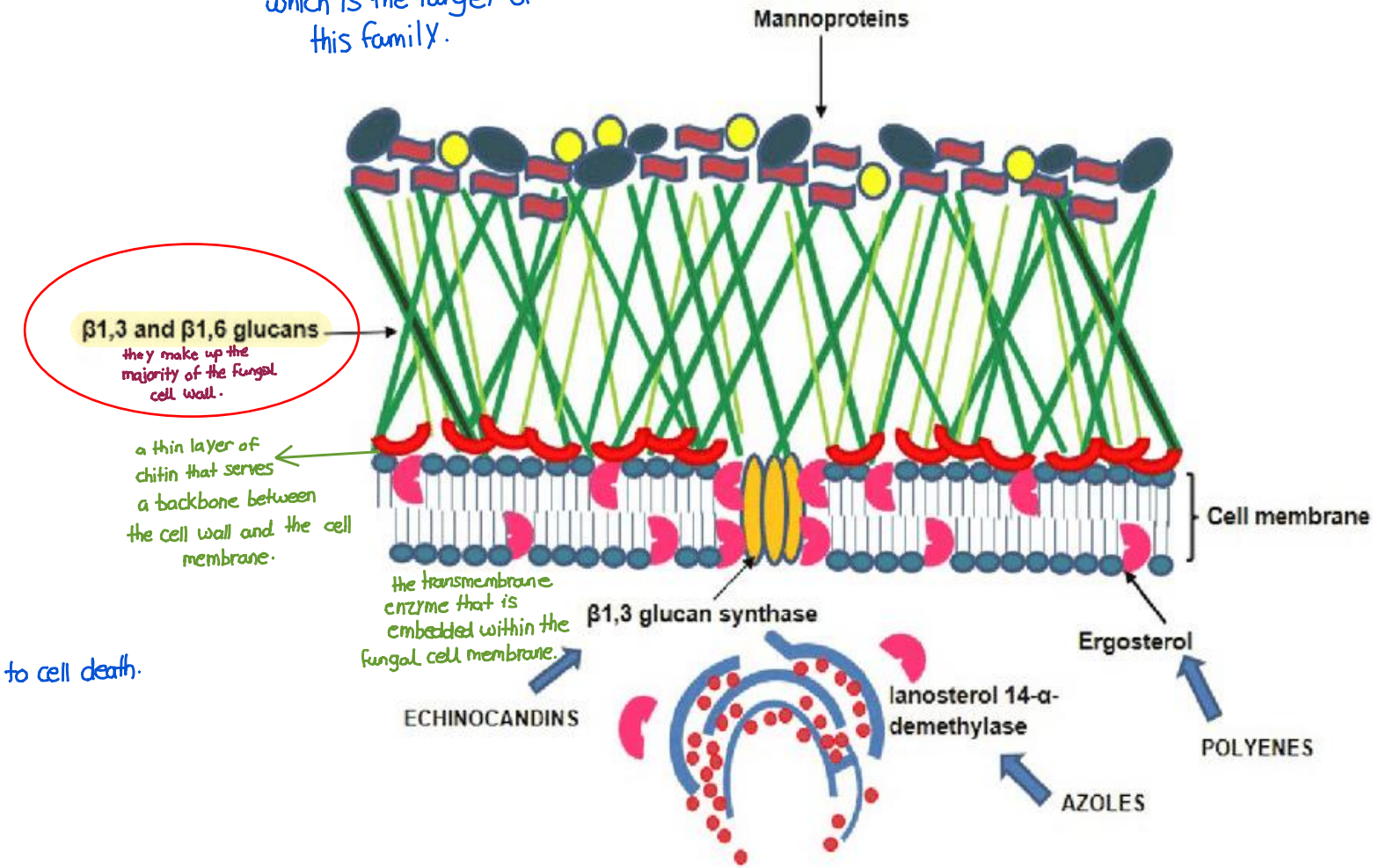
* the composition is different
  - the bacterial
    * peptidoglycan precursors, then getting cross-linked through the PBPs.
  - the fungal
    * is resistant to the bacterial cell wall inhibitors.
    * made of glucans and chitin precursors.

Echinocandins

this family inhibits the β1,3-D-glucan synthase which is the target of this family.

Mechanism of action

- Inhibit the synthesis of *β(1,3)-D-glucan synthase* → inhibit β(1,3)-D-glucan synthesis → inhibit cell wall synthesis thus leading to cell death.



* Caspofungin requires a loading dose then we can give it a seperate multiple doses after that.

* Caspofungin is metabolized by the CYP450 system is also associated with hepatotoxicity, it's bigger and worse when caspofungin is given with another hepatotoxic drug.

Caspofungin

- First-line for patients with invasive candidiasis e.g., candidemia

a systemic infection caused by the candidia.

- Second-line for invasive aspergillosis

so if the first line drug to treat aspergillosis is inhibited for any reason, then the caspofungin is then used.

- Must be administered by slow IV infusion because it can cause histamine-like reaction

such as the amphotericin B than can cause intense chills and fevers after the infusion.

- MUST NOT be given with cyclosporine → hepatotoxicity

the risk of hepatic injury "usually in the form of elevated hepatic transaminases"

Micafungin and Anidulafungin

doesn't require a loading dose.

- First-line options for the treatment of invasive candidiasis e.g., candidema
  like patients with HIV and immune deficiency and can develop an esophageal infection by candidia called the esophageal candidiasis
  *this infection usually don't happen in healthy people.
- Prophylaxis against candida infections in patients undergoing organ transplant
  in immuno suppressed patients
  the organ transplant processes, those patients receive immunosuppresion therapy to accept the newly transplanted organ.
- No drug-drug interactions
  because it's not metabolized by the hepatic enzymes.

Drugs For Cutaneous Mycotic Infections

* certain types of fungi can cause both infections: the systemic and the cutaneous infections.
like candida

* important info:
when we talk about the first line of treating candida were talking about the invasive systemic candida, but local infections like skin infections caused by candida are treated by the cutaneous drugs.

DRUGS FOR CUTANEOUS MYCOSES

Butenafine LOTRIMIN ULTRA
Butoconazole GYNAZOLE
Clotrimazole LOTRIMIN AF
Ciclopirox PENLAC
Econazole ECOZA
Griseofulvin GRIFULVIN V, GRIS-PEG
Miconazole FUNGOID, MICATIN, MONISTAT
Naftifine NAFTIN
Nystatin MYCOSTATIN
Oxiconazole OXISTAT
Sertaconazole ERTACZO
Sulconazole EXELDERM
Terbinafine LAMISIL
Terconazole TERAZOL
Tioconazole VAGISTAT-1
Tolnaftate TINACTIN

Drugs For Cutaneous Mycotic Infections

those infections are usually common and not only related to the immunocompromised patients.

- Dermatophytes/tinea
- Classified according to affected site, e.g., tinea pedis
- Main fungal classes that cause cutaneous infections:

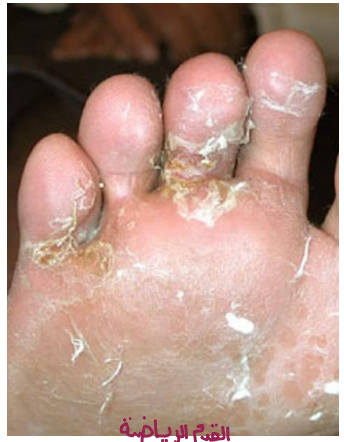
1. Trichophyton
2. Microsporum
3. Epidermophyton

they can cause a varity of skin infections, the skin infections are named according to its place.

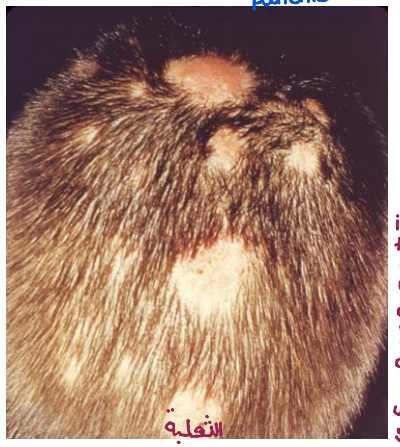
*tenia corporis
*tenia versicolor

all of them require the treatment with an antifungal drugs.

those aren't dangerous but they're still contagious.

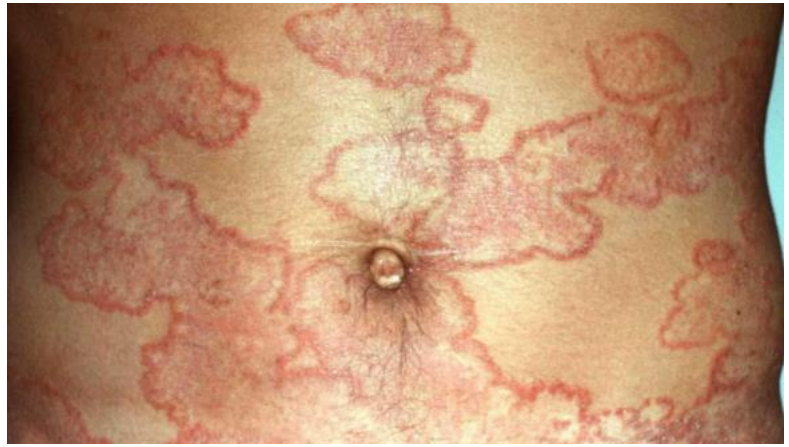


tinea pedis



tinea capitis

infection of the hair scalp that usually destroys the hair follicles and is reversible with a significant hair loss.



it's not the same as the ring worm.

tinea corporis

fungal infections on the trunk

Wolters Kluwer

Squalene Epoxidase Inhibitors

Squalene Epoxidase Inhibitors

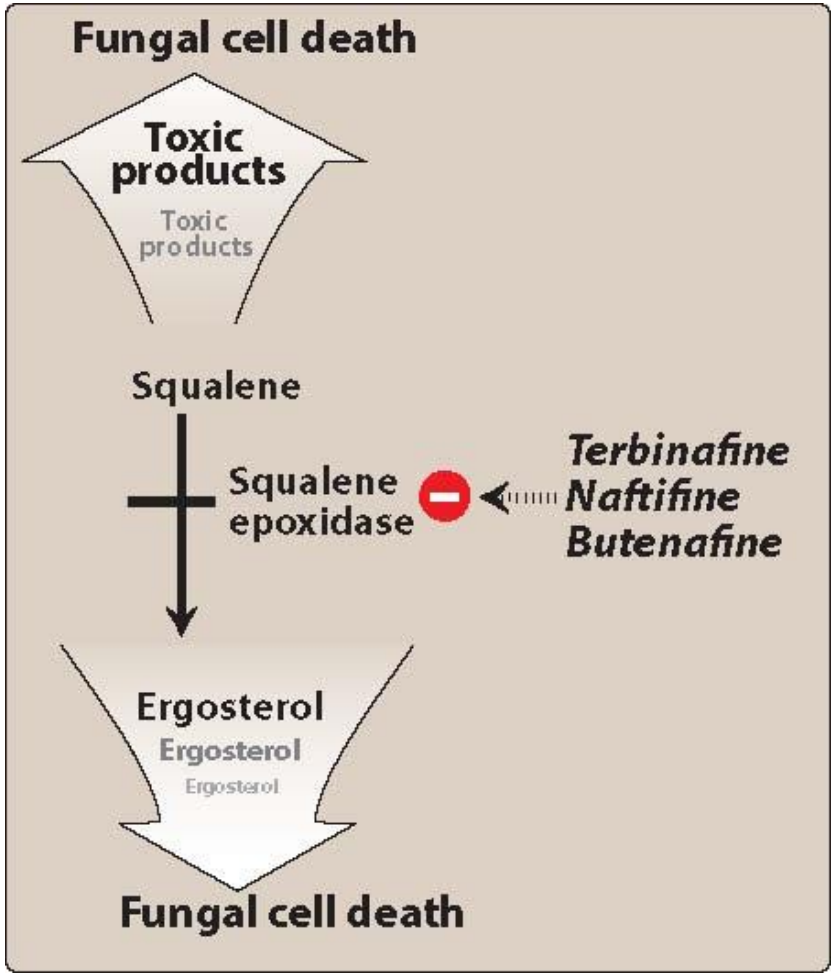
the target is the squalene epoxidase enzyme that is a part of the biosynthesis of ergosterol.

Mechanism of action

- Inhibition of *squalene epoxidase*
- Blocking the biosynthesis of ergosterol
- Squalene accumulation affects membrane permeability

injury to multiple membrane structures, by increasing the permeability and the leakage of the cell's components to the outside.

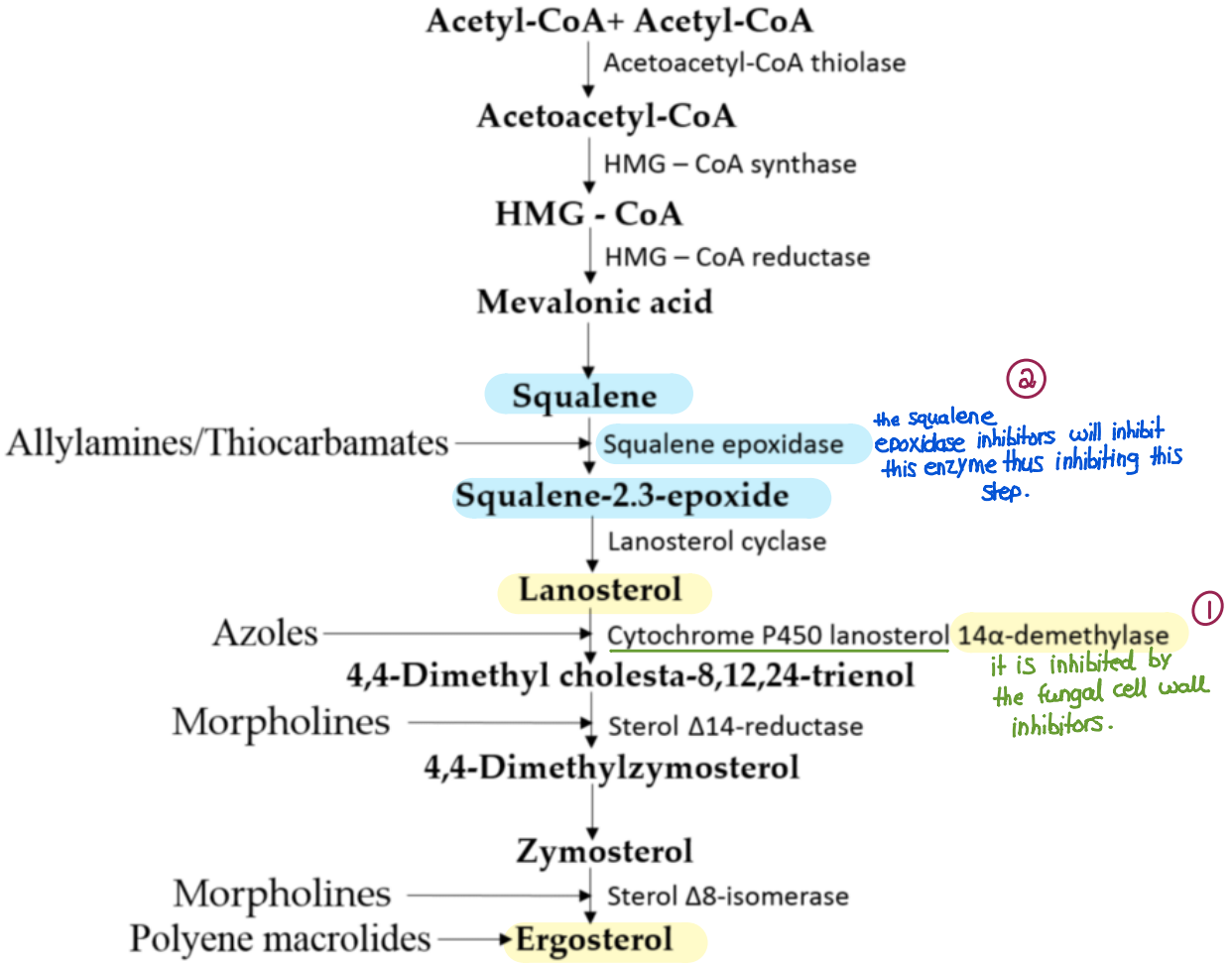
squalene is known to be toxic so if it starts to accumulate at high levels will become toxic to the fungal cells.



Remember that the ergosterol is an important substance in the cell wall of the fungi.

Ergosterol Synthesis

a complicated biochemical pathway.



Most of the cutaneous infections must be treated by systemic drugs like the orally given drugs.

حتى كلام الأمراض السطحية تتعالج بأدوية سطحية أبدًا .

skin fungal infections may take months or years.

1. Better tolerated due to the toxicity.
2. Short duration of therapy.
3.

Terbinafine

- Drug of choice for treating dermatophyte onychomycoses
- More effective than itraconazole or griseofulvin for Trichophyton

requires 6-12 months

- Useful in the treatment of tinea capitis

more preffered

-oral terbinafine (topical ineffective)

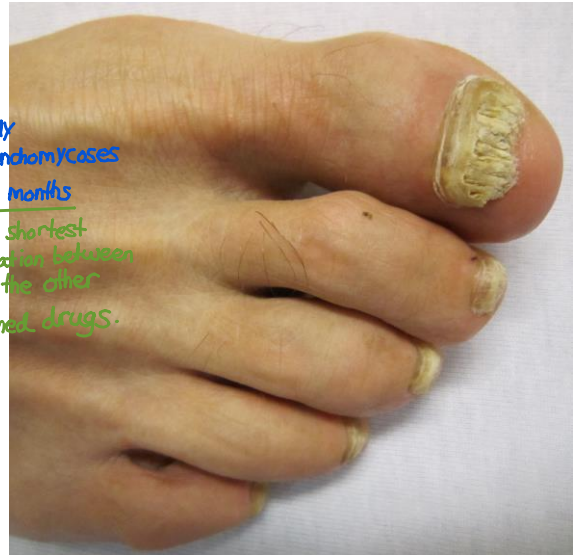
in the tinea capitis, we have to use the oral form of terbinafine because the topical form is ineffective.

to be directly applied on the site of infections.

-topical can be used with other types, e.g., pedis, corporis…

as we said that depending on the site of infection we name those infections, this infection mentioned here is limited to the nails as shown in the picture below.

very short therapy duration which is relatively to other drugs, if we want to treat the onchomycoses by oral terbinafine, then we will need 3 months the shortest duration between all the other mentioned drugs.



dermatophyte onychomycosis (fungal infection of the nail)

Terbinafine

Oral treatment is prolonged (months)

Antifungal spectrum

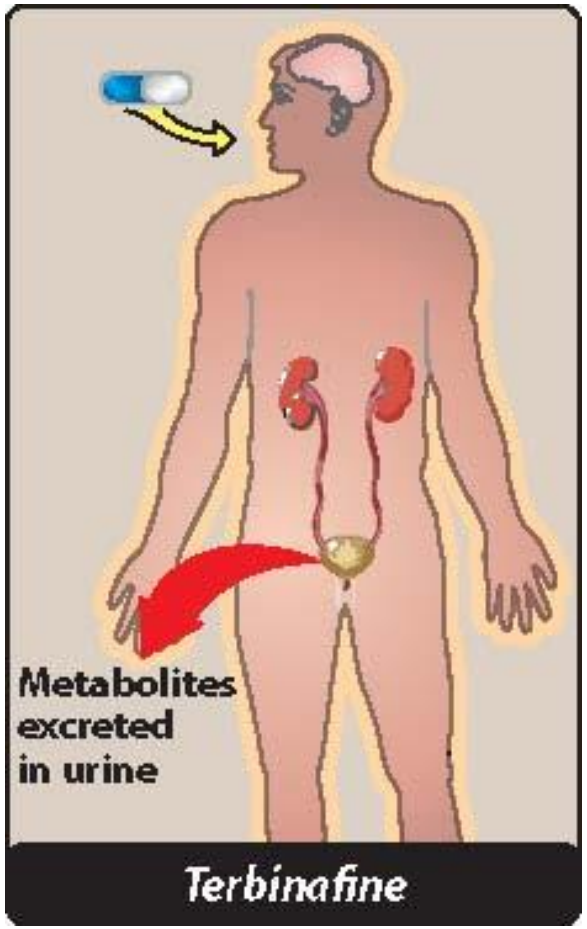
- Effective against: Trichophyton, Candida, Epidermophyton, Scopulariopsis

because it can cause localized infections.

Pharmacokinetics

- Oral and topical
- Prolonged half-life (200-400 h). Why?
- Extensively metabolized by CYP450 and excreted renally
- Potent inhibitor of CYP2D6

so when we have to combine terbinafine with other drug that is metabolized by CYP2D6, we have to adjust the dose of that drug.



Griseofulvin

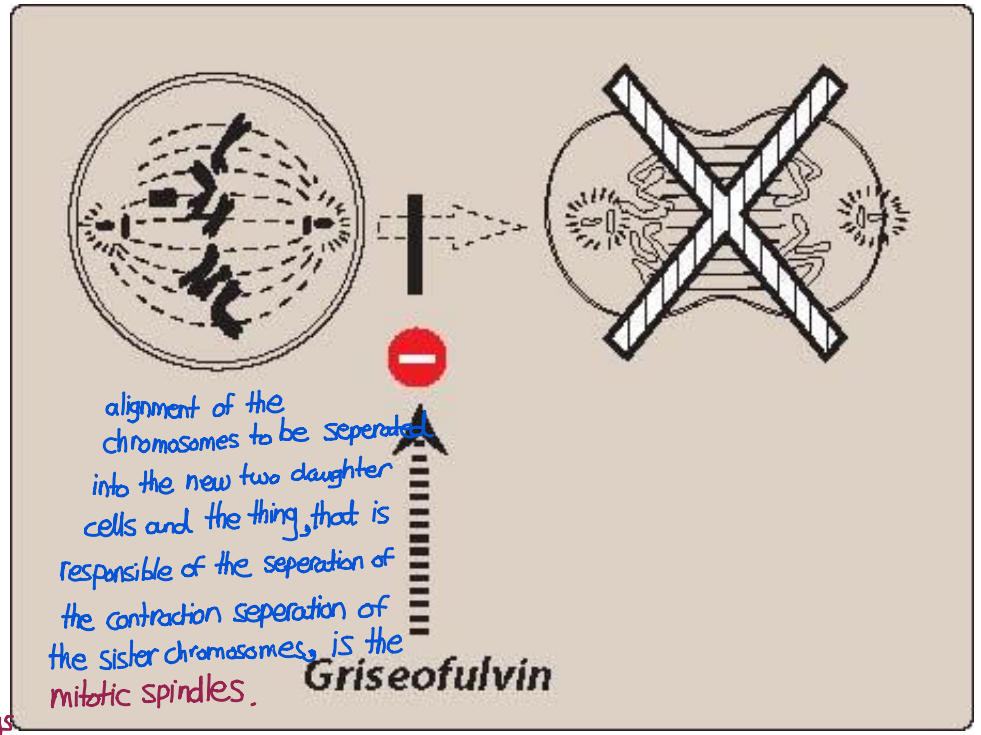
the fungal cells are like the mammalian cells, go under the different phases of the cell cycle, and they enter the G1 phase then to the S phase where they replicate their DNA then the G2 phase for cell division to be ready to the M phase.
to divide to 2 daughter cells

Griseofulvin

is still given orally with high concentrations in nails, hair and adipose tissues.

- **MOA**: disruption of the mitotic spindle and inhibition of fungal mitosis
- Has been largely replaced by oral terbinafine for nail infection
- Still used to treat dermatophytosis of the scalp and hair
- Fungistatic
- Requires long duration of treatment. Why? its duration depends on the formation of new nails, and the complete cure of infection occurs when there's a replacement of the infected nail with a new, normal and healthy nail.
- INDUCES hepatic CYP450 activity — it will increase the metabolism of other drugs and lowering its plasma concentration.
- Contraindicated in pregnancy and porphyria patients

فأنا هنا السواء ح أزيد من جرعته عشان هو ح تزيد سرعة عملية أيضه.

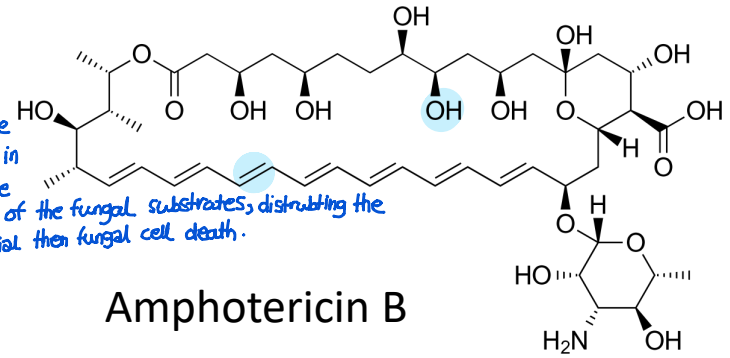


Nystatin

Nystatin

- Polyene
- Very similar to amphotericin B
- Used for the treatment of oral and cutaneous Candida
- **Routes:**

this tells us that Nystatin has the same MOA to amphotericin B , which can make hydrophobic interactions with the ergosterol leading the creation of pores in the cell membrane then the leakage of the fungal substrates, distrubting the fungal cell potential then fungal cell death.



Amphotericin B

- ❑No parenteral use (toxic)
- ❑Orally ("swish and swallow" or "swish and spit")
- ❑Intravaginally
- ❑topically

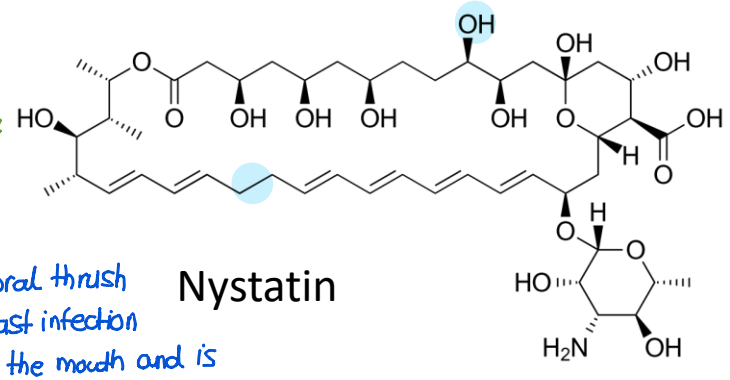
has poor oral absorption, thus isn't very effective in treating the systemic infections like treating the meningitis.
"isn't absorbed from the gut"

to treat the vaginal candidiasis

for the treatment of cutaneous candidial infections.

the liquid preperation of the nystatin is like rinsing "غرغرة".

in the cases of local fungal infection in the mucous membrane of the oral cavity.



Nystatin

like the oral thrush when a yeast infection develops in the mouth and is also called the oral candidiasis.

*Nystatin is a very toxic compound when given IV and is associated with nephrotoxicity. more severe than amphotericin B.

Azole Antifungals

interefers with the ergosterol synthesis by the inhibition of the cyp450 fungal enzyme.

Imidazole Antifungals

are used to treat cutaneous fungal infections.

Triazole Antifungals

used to treat systemic fungal infections.

ممكن برفه أستخدمهم لعلاج الـcutaneous
مثل الـintraconazole اللي هو يستخدم لعلاج الـsystemic
وبرفه لعلاج الـcutaneous.

Imidazoles

- **Drugs**:

- ❑Butoconazole
- ❑Clotrimazole
- ❑Econazole
- ❑Ketoconazole
- ❑Miconazole
- ❑Oxiconazole
- ❑Sertaconazole
- ❑Sulconazole
- ❑Terconazole
- ❑Tioconazole

an old drug.

Imidazoles

- Wide range of antifungal activity
- Still used topically for the treatment of tinea corporis, tinea cruris, tinea pedis, and oropharyngeal and vulvo-vaginal candidiasis
- Miconazole: available as a buccal tablet
- Clotrimazole: available as throat lozenge
- Ketoconazole: historically used for systemic mycoses (highly toxic –causes severe liver injury)

جلّ داخل الفمّ زي حبرأ مجون الأسنان.

now is used topically to treat cutaneous infections.

ممكن شاجبوه كريمات ، جلّ ال

Ciclopirox

Ciclopirox

- **MOA**: Inhibits transport of essential elements in the fungal cell

like amino acids
nitrogeous bases

- Disrupts synthesis of DNA, RNA and proteins
- Available as a shampoo for seborrheic dermatitis
- Available as a gel/cream for Tinea pedis, tinea corporis, tinea cruris, cutaneous candidiasis, and tinea versicolor

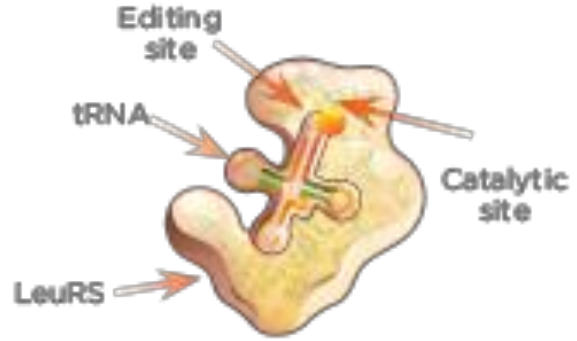
Tavaborole

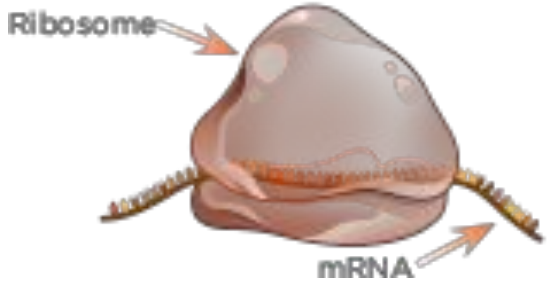
Tavaborole

- **MOA**: inhibits fungal aminoacyl-transfer ribonucleic acid synthetase → inhibition of fungal protein synthesis

which is a function of the fungal ribosome.

- Can be used for the treatment of toenail onychomycosis (requires 48 weeks of treatment)





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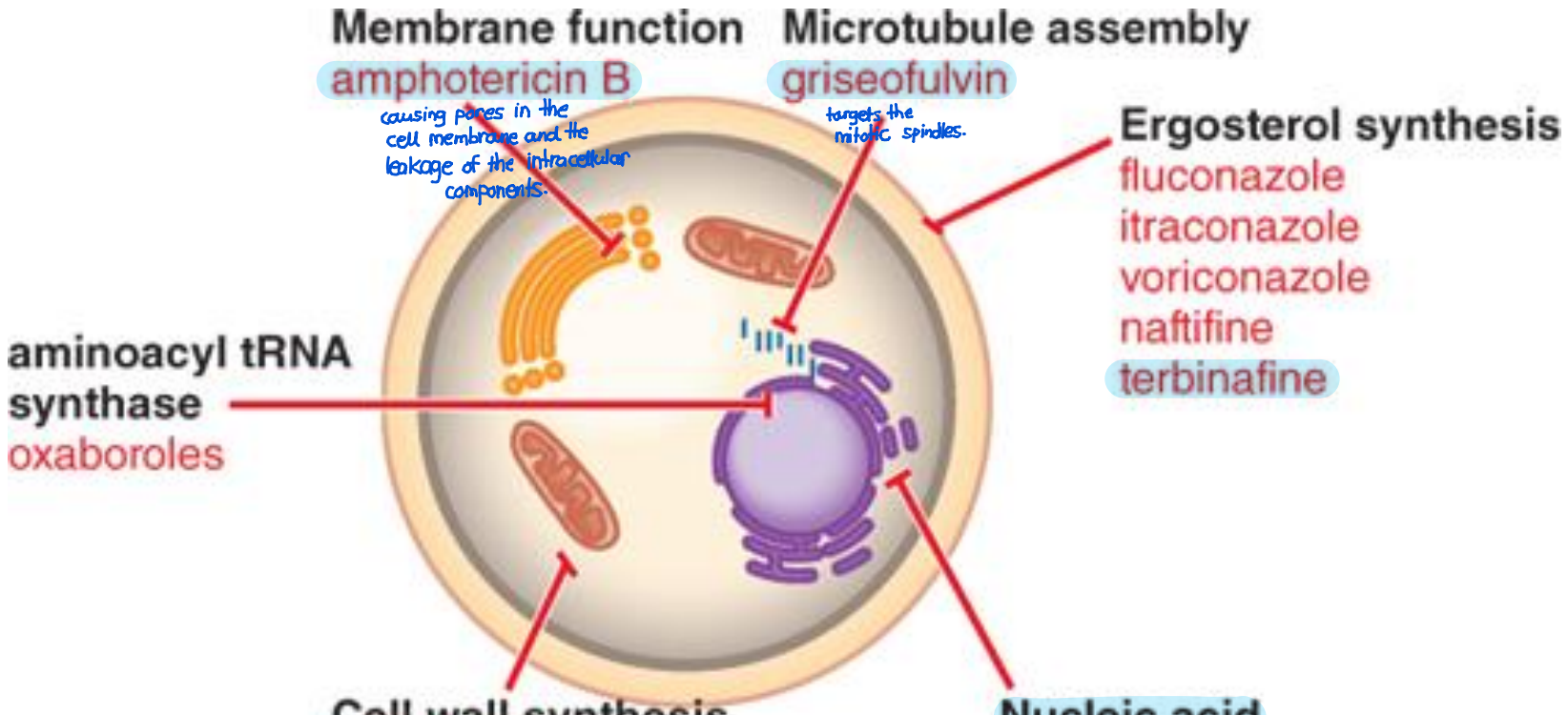
Summary



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You are a physician-scientist in a drug development company. You are leading a research group investigating the development of potent antifungal drugs. Due to decreased funding, the company asked you to stop one of the undergoing projects by your team. Which project will you stop?

(A) Development of drug A – a potent inhibitor of fungal DNA synthesis

(B) Development of drug B – activator of fungal CYP450 microsomal enzymes

(C) Development of drug C – inhibitor of fungal aminoacyl-transfer ribonucleic acid synthetase

(D) Development of drug D – inhibitor of fungal *β(1,3)-D-glucan synthase*

(E) Development of drug E – inhibitor of chitin polymerization