ANTIFUNGAL DRUGS

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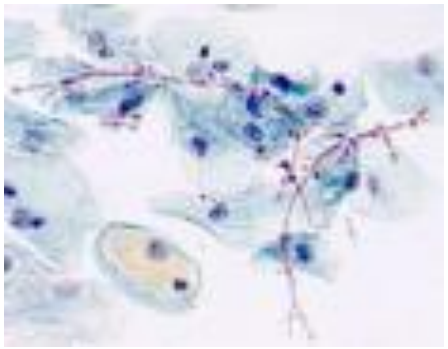
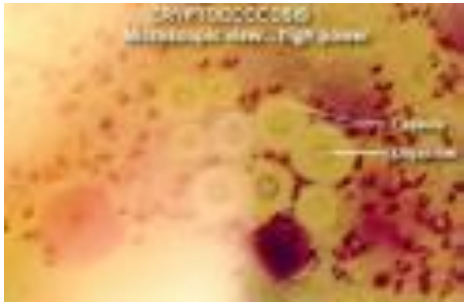
Fungal infections

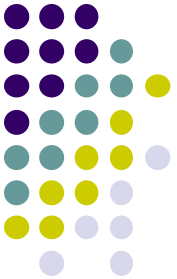


Candida albicans



Cryptococcosis

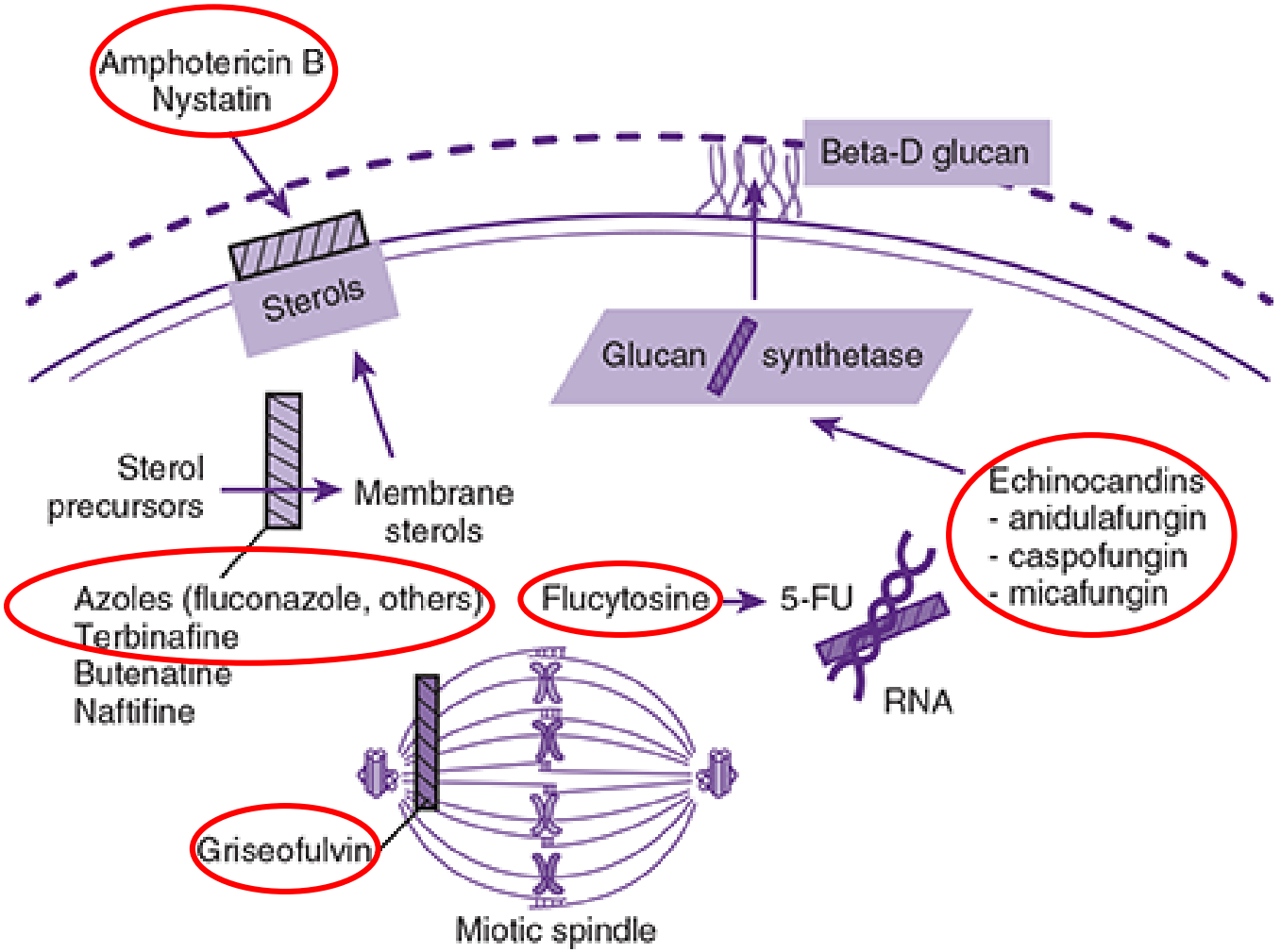
ANTIFUNGAL DRUGS



Group	Substance
POLYENES	*Amphotericin B* *Nystatin*
AZOLES	*Clotrimazole* *Miconazole* *Ketoconazole* *Fluconazole* *Itraconazole*
ECHINOCANDINS	*Anidulafungin* *Caspofungin* *Micafungin*
ALLYLAMINES	*Terbinafine*
OTHER	*Flucytosine* *Griseofulvin*

ANTIFUNGALS

General MOA



Source: Charles D. Ciccone: *Pharmacology in Rehabilitation*, 5th Edition:
www.FADavisPTCollection.com

POLYENES

Mechanism of action

Amphotericin B

↓

Binds ergosterol in fungal cell membrane

↓

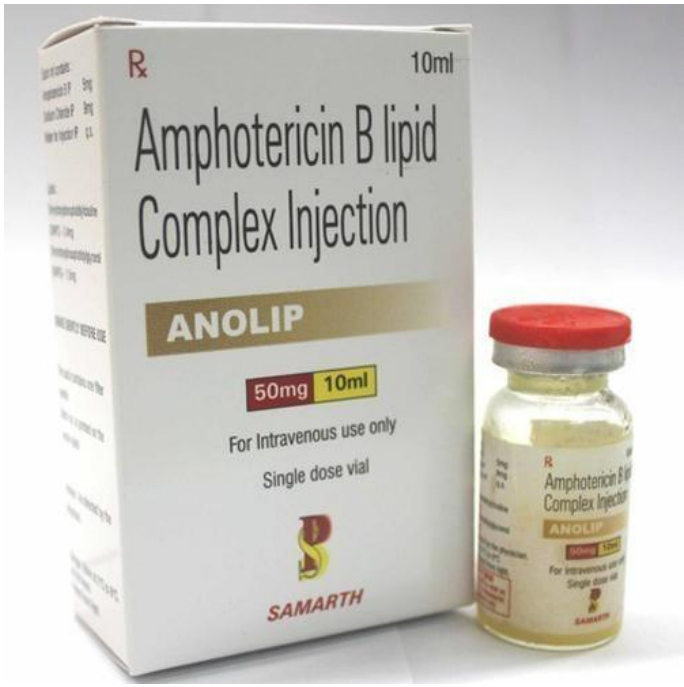
Form pores in cell membrane

↓

Cell contents leak out

↓

Cell death



- **ergosterol** (basic component of fungal membrane)
  - permeates into ergosterol-rich membranes & produces a **detergent-like effect (micropores)**

POLYENES
PK



Amphotericin B – p.o., i.v., intrathecal

- **poor GI absorption**
- **bad CNS penetration** (intrathecal route)
- **oral absorption ⇑ with milk, fat ingestion**
- **concentration in skin, hair, nails**

Nystatin **– oral, vaginal, topical**

POLYENES

Indications

AMPHOTERICIN

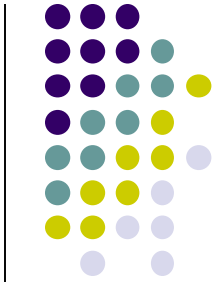
- **generalised fungal infections**

(Candida; Aspergillus; Histoplasma; Cryptococcus; Rhizopus; Sporothrix)

NYSTATIN

- **oral in GI mycosis**
- **local:**
  - **skin, mucosa**
  - **vaginal mycosis**

POLYENES
SE



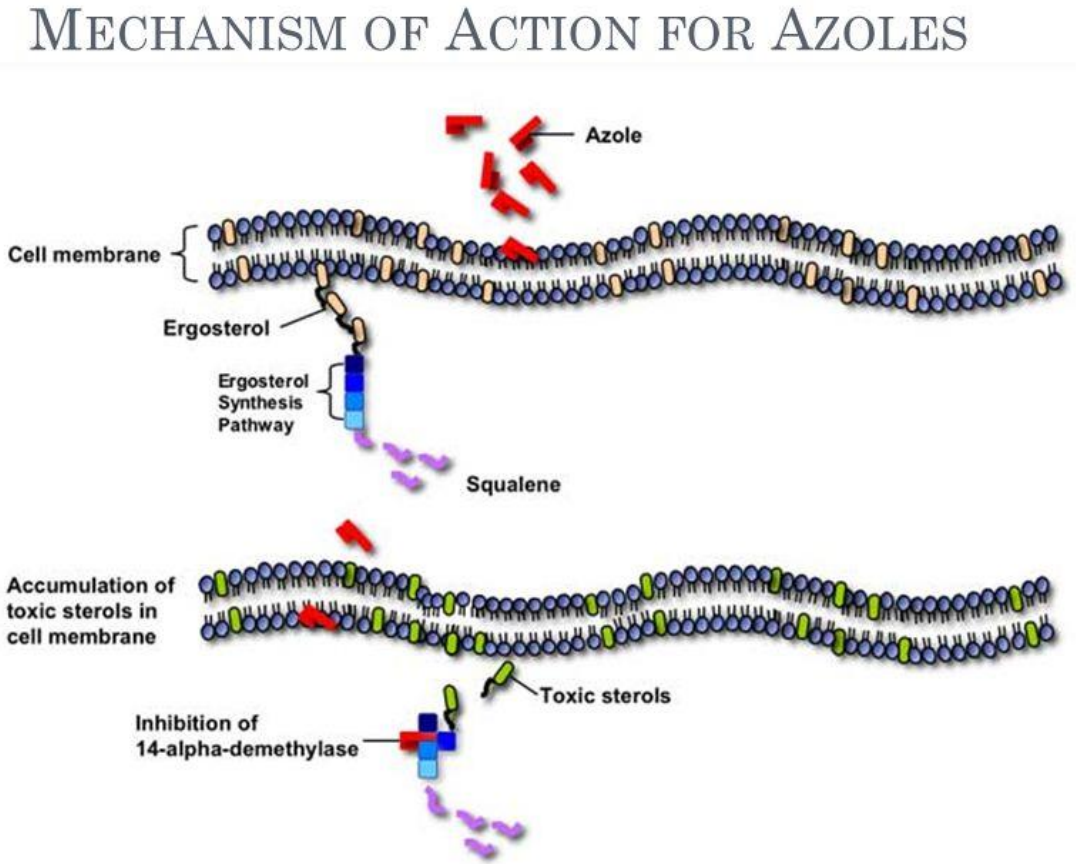
AMPHOTERICIN B

- **nephrotoxicity** (major dose-limiting adverse effect)
- ⇓ glomerular filtration; renal tubular acidosis
- hypokalemia, hypomagnesemia
- **i.v. infusion: fever, chills, rigors, hypotension** („shake & bake“ reaction)
- **anaemia** (via ⇓ erythropoietin)

NYSTATIN

- **oral & local: no side effects**

AZOLES



Prevent ergosterol synthesis from lanosterol by:

- ⇓ fungal CYP450-dependent 14-α-demethylation

AZOLES

PK

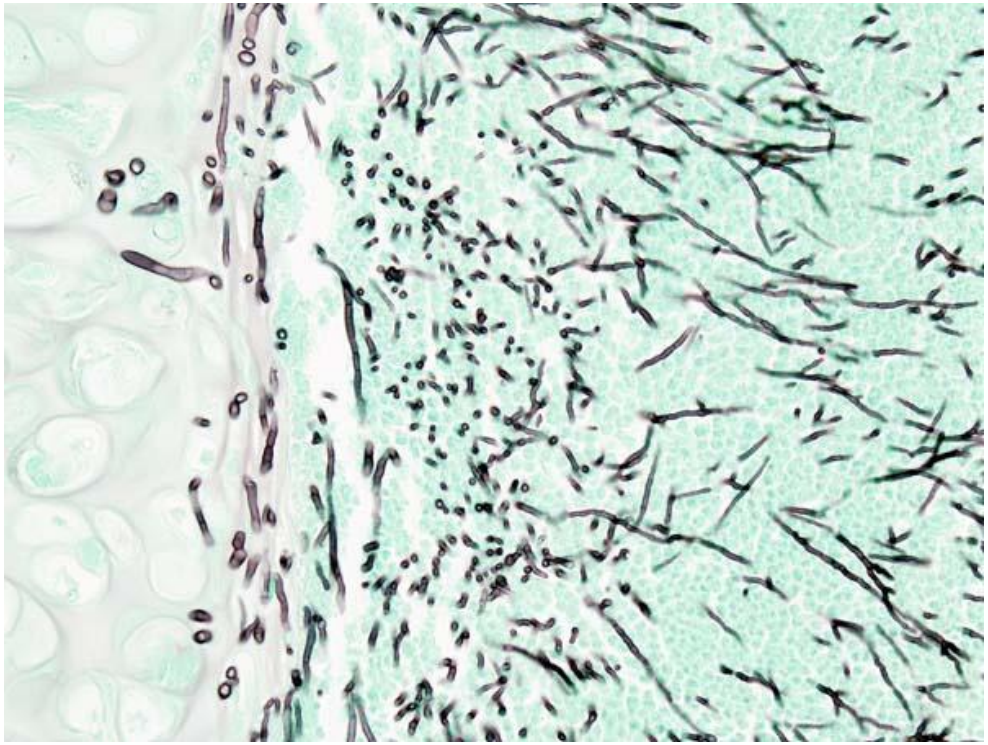
- **Oral absorption** ⇓ by **alkalinization** of gastric pH

  (ketoconazole + antacids)

- **Oral absorption** ⇑ with **acidic** beverages

  (containing phosphoric or citric acids - Coca-Cola; Pepsi-Cola)

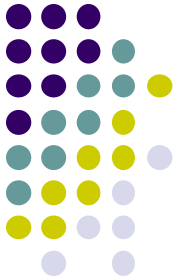
- **Good tissue diffusion**



Pulmonary invasive aspergillosis

AZOLES

Indications



Drugs of choice in:

FLUCONAZOLE

- mucocutaneous candidiasis
- coccidioidomycosis
- cryptococcal meningitis (prevention & treatment)

ITRACONAZOLE

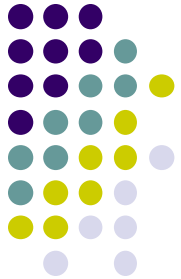
- sporotrichoses
- blastomycoses

KETOCONAZOLE

- paracoccidioides
- dermatophytosis of the scalp (tinea capitis – shampoo)

OTHER AZOLES

Indications



Mainly for local (topical) **use:**

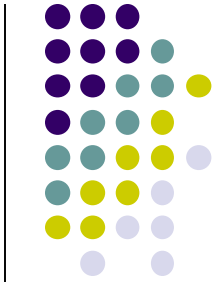
MICONAZOLE

- **mucocutaneous candidiasis** as oral gel, oinment
- **vaginal mycoses** - cream, tbl.

CLOTRIMAZOLE

- to treat & prevent ***Candida*** (yeast) infections of the mouth & throat or other skin or mucosal areas
- in a form of troches, vaginal tbl. (suppositories), oinment, cream, gel

AZOLES
SE



All azoles:

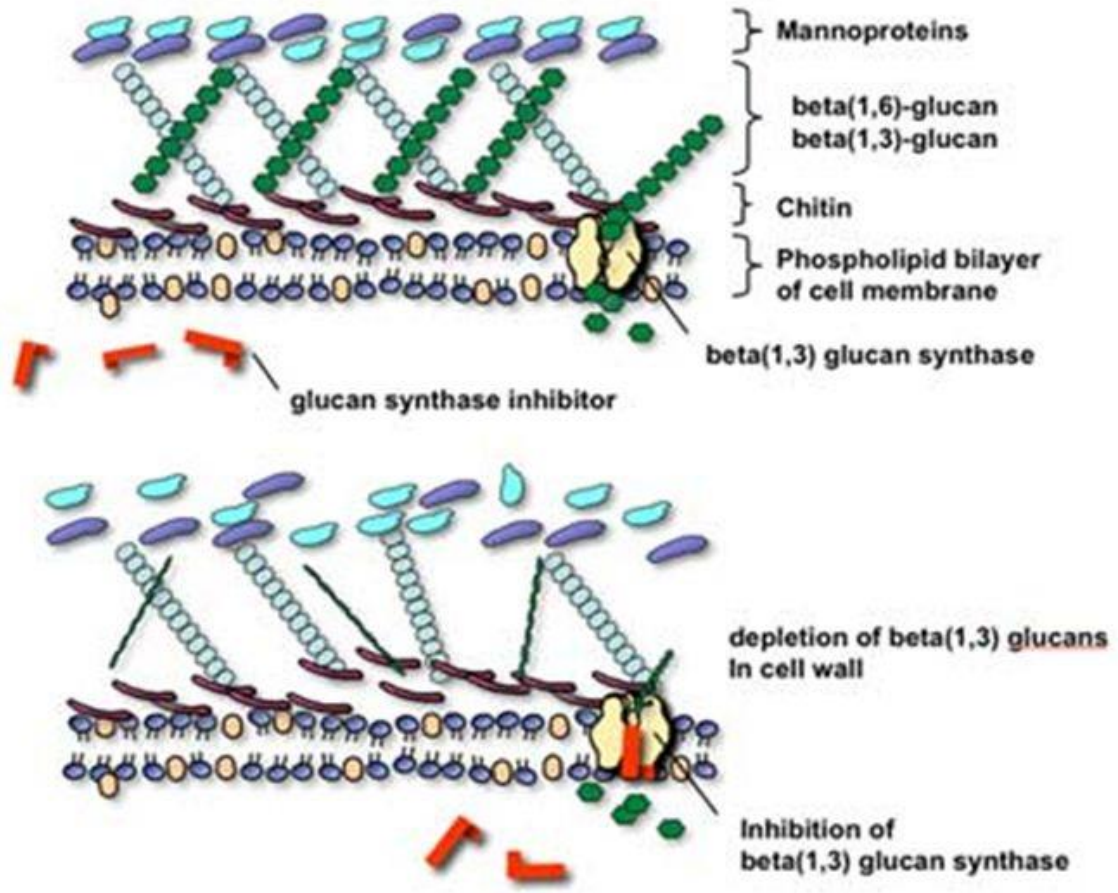
- **elevated liver function tests** (hepatotoxicity)
- rare GI problems; nausea
- skin intolerance
- headache

KETOCONAZOLE

- **gynecomastia** (via ⇓ of androgen synthesis)
- ⇓ glucocorticoid synthesis

ECHINOCANDINS

MECHANISM OF ACTION FOR ECHINOCANDINS



ECHINOCANDINS

PK

Anidulafungin

- **i.v. only** (infusion)
- strong protein binding (> 99%)
- slow chemical degradation (no inhibition or induction of CYP450)
- partial feces elimination (no urinary elimination)

Micafungin

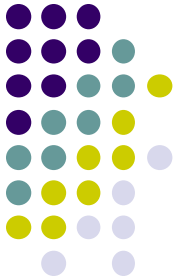
- **slow i.v. infusion**
- strong protein binding (> 99%)
- fast tissue distribution
- several metabolites (with no therapeutic effect)

Caspofungin

- **slow i.v. infusion**
- strong protein binding
- tissue distribution (92% in 2 days)
- spontaneous degradation (no CYP450 inhibition)

ECHINOCANDINS

Indications



Anidulafungin (only in adults)

- treatment of **invasive *candidiasis***

Caspofungin (both in adult & pediatric patients)

- treatment of **invasive *candidiasis***
- treatment of **invasive *aspergilosis*** in patients refractory to *amphotericine B*
- **empirical** treatment of possible mycotic infections in febrile, neutropenic patients

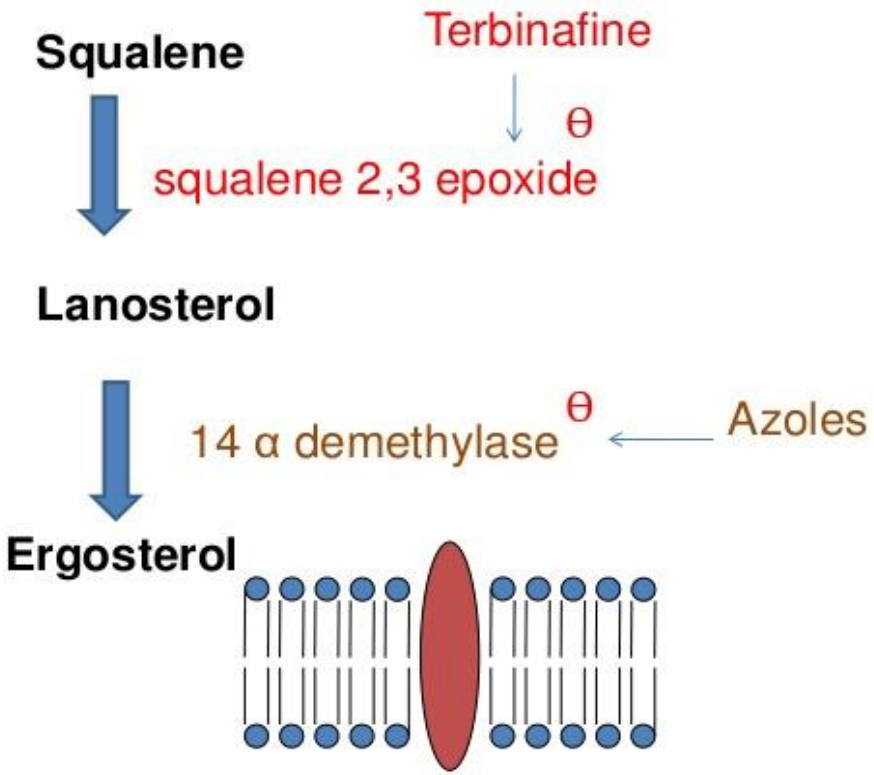
Micafungin (adults & ≥ 16 y)

- treatment of **invasive *candidiasis***
- treatment of **esophageal *candidiasis***
- **prophylaxis of *candidiasis*** in patients with allogenic transplantation of hematopoetic stem cells

ALLYLAMINES

TERBINAFINE

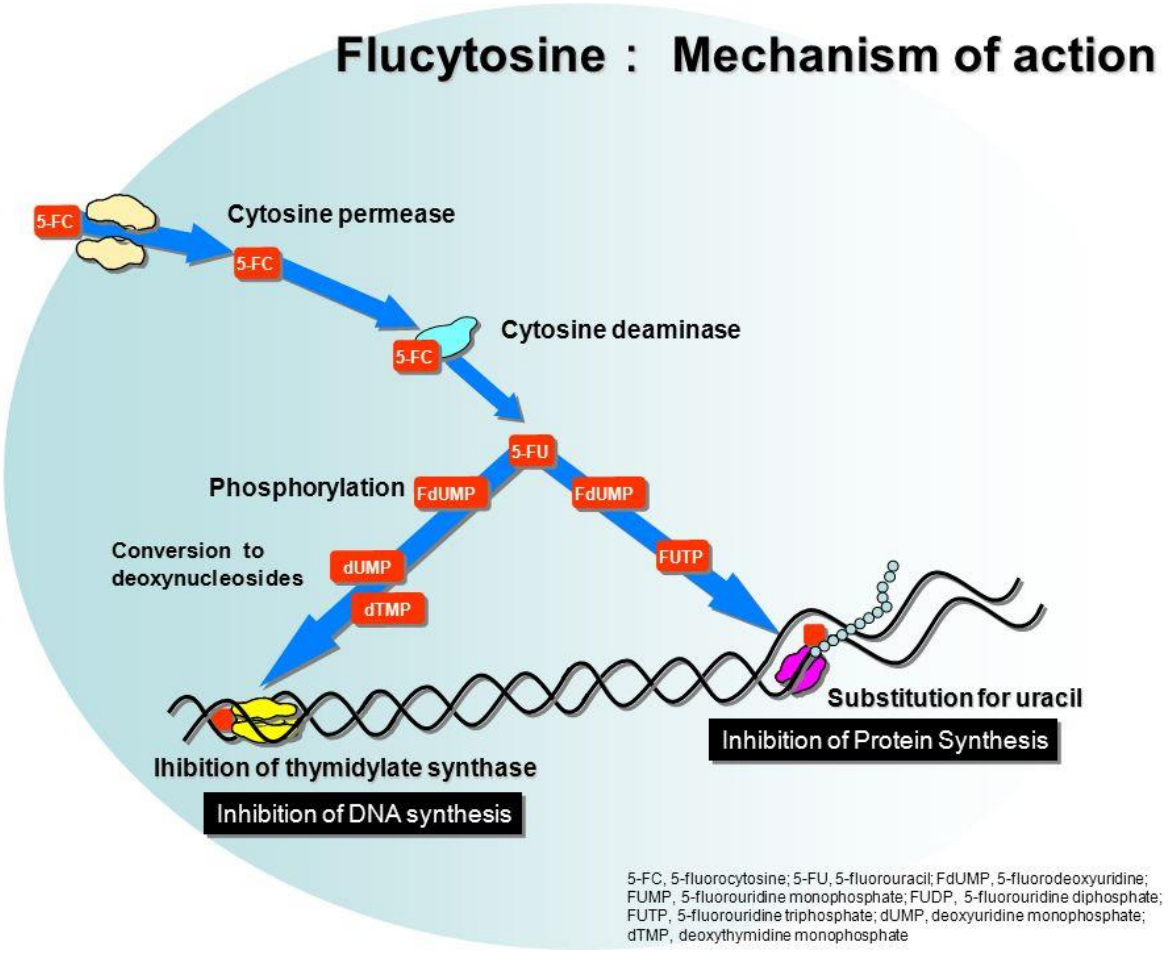
Mechanism of action:



- ⇓ **ergosterol synthesis** by *squalene epoxidase* ⇓
- **oral application** (or topical)
- **useful in dermatophytic infections; specific types** (onychomycosis of the toenail & fingernail)
- **hepatotoxicity** (major dose-limiting adverse reaction)

OTHER ANTIFUNGAL DRUGS

FLUCYTOSINE



- converted to **5-FU** (**fungal** cytosine deaminase - **mammalian cells cannot convert it)**
- ⇓ **DNA & RNA synthesis**
- synergistic with ***amphotericin B*** *(Candida; Cryptococcus)*
- **useful as systemic antifungal drug**

OTHER ANTIFUNGAL DRUGS

GRISEOFULVIN

MECHANISM OF ACTION

GRISEOFULVIN

↓ Binds to

Tubulins

↓ inhibiting

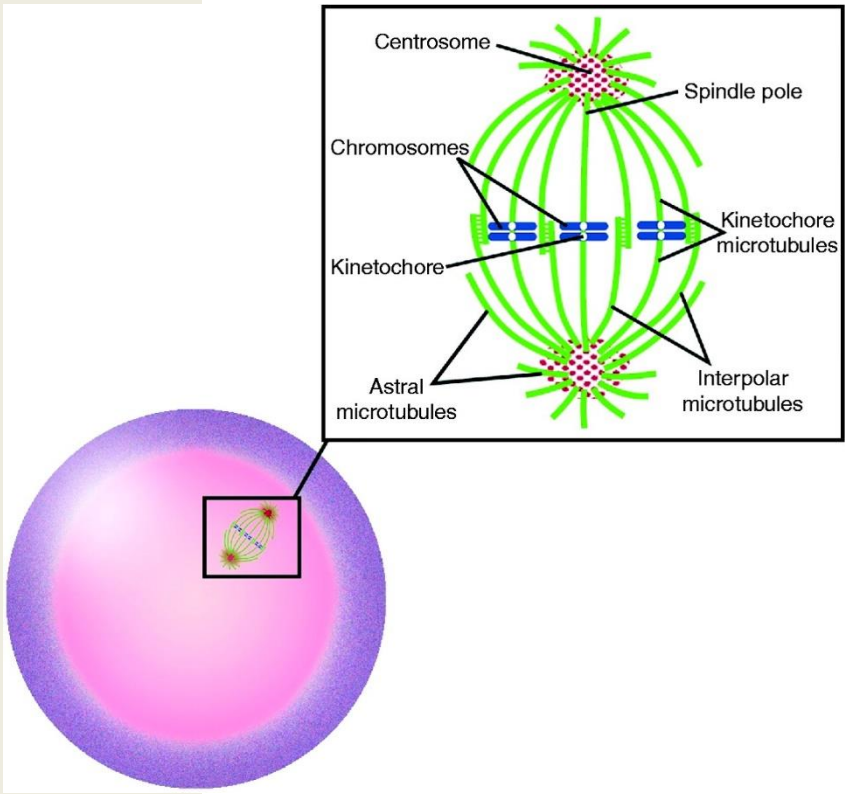
Mitotic spindle formation

↓ Resulting in

Inhibition of separation of daughter nuclei

↓

FUNGISTATIC EFFECT



OTHER ANTIFUNGAL DRUGS

PK

FLUCYTOSINE

- good absorption
- good CNS penetration (75%)
- renal elimination in unchanged form

GRISEOFULVIN

- high-fat meals enhance GI absorption
- eliminated by urine (up to 50%) & feces

OTHER ANTIFUNGAL DRUGS

Indication & SE

FLUCYTOSINE

- **systemic candidiasis**
- **septicemies**

Side effects:

- GIT
- haematologic
- hepatal

GRISEOFULVIN

- **only against dermatophytes**

Side effects:

- **hepatotoxicity** (dose-limiting adverse effect)
- contraindicated in acute intermittent porphyria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