Antifungals

Systemic & Topical

Some are fungistatic,
while others are fungicidal

An **antifungal medication** is a pharmaceutical fungicide used to treat and prevent mycoses such as athlete's foot,ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others. Such drugs are usually obtained by a doctor's prescription, but a few are available OTC (over-the-counter).

Fungal Infection in Humans = Mycosis

- Major Types of Mycoses
  - superficial
  - cutaneous
  - subcutaneous

    systemic infection

Antifungal Agents

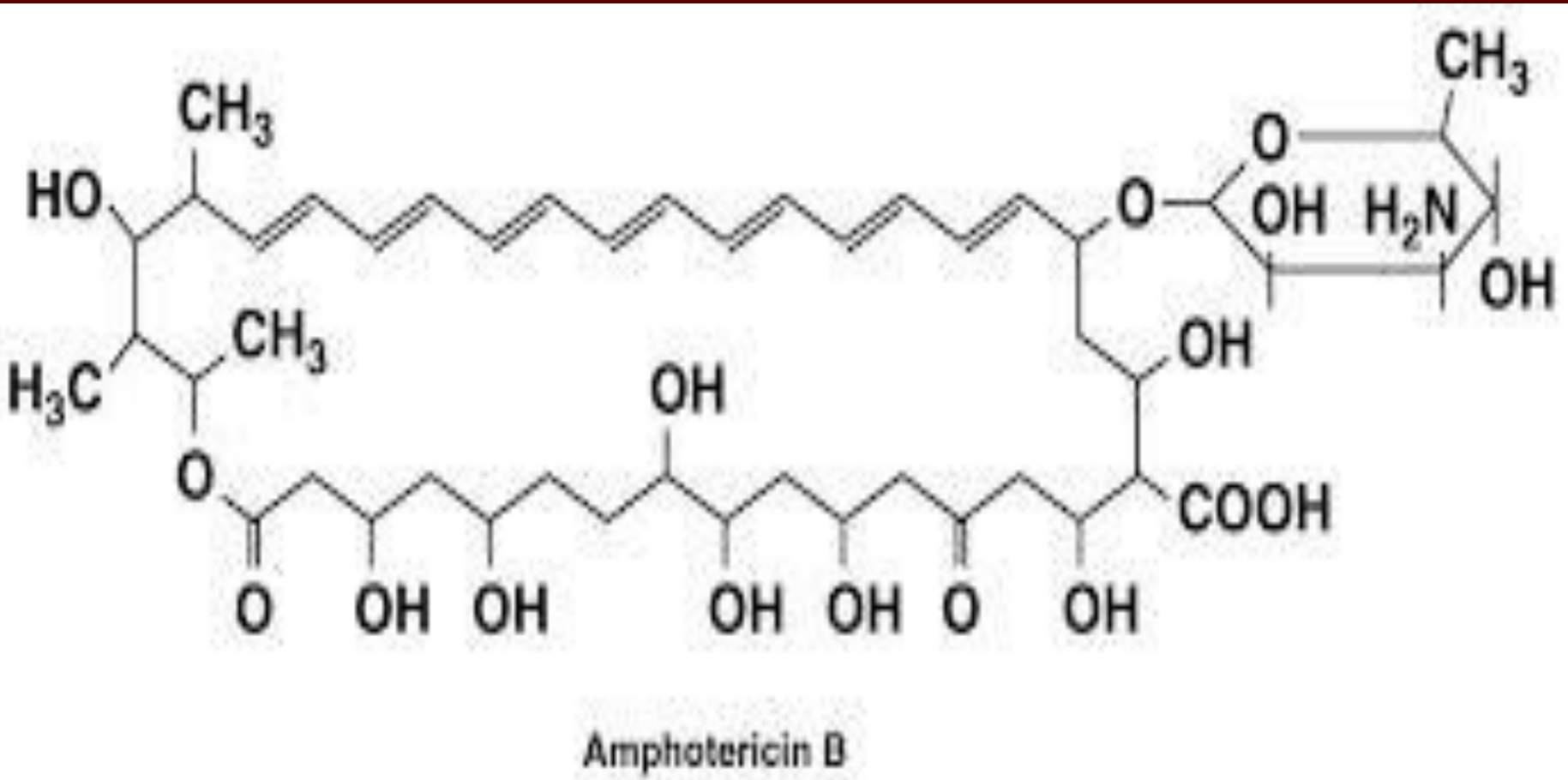
- **1. Antibiotics**
- *A. Polyenes:* AmphotericinB (AMB),Nystatin, Hamycin, Natamycin (Pimaricin)
- B. *Heterocyclic benzofuran*: Griseofulvin
- **2. Antimetabolite :** Flucytosine (5-FC)
- **3 Azoles :**
- *A. Imidazoles (topical):* Clotrimazole,Econazole, Miconazole, Oxiconazole
- *(systemic):* Ketoconazole
- *B. Triazoles (systemic):* Fluconazole,Itraconazole,Voriconazole

Note : Nystatin- The first antibiotic against fungi

- *4. Allylamine :* Terbinafine
- *5. Other topical agents*
- Tolnaftate, Undecylenic acid, Benzoic acid,
- Quiniodochlor, Ciclopirox olamine, Butenafine,
- Sod. thiosulfate.

POLYENE ANTI BIOTICS

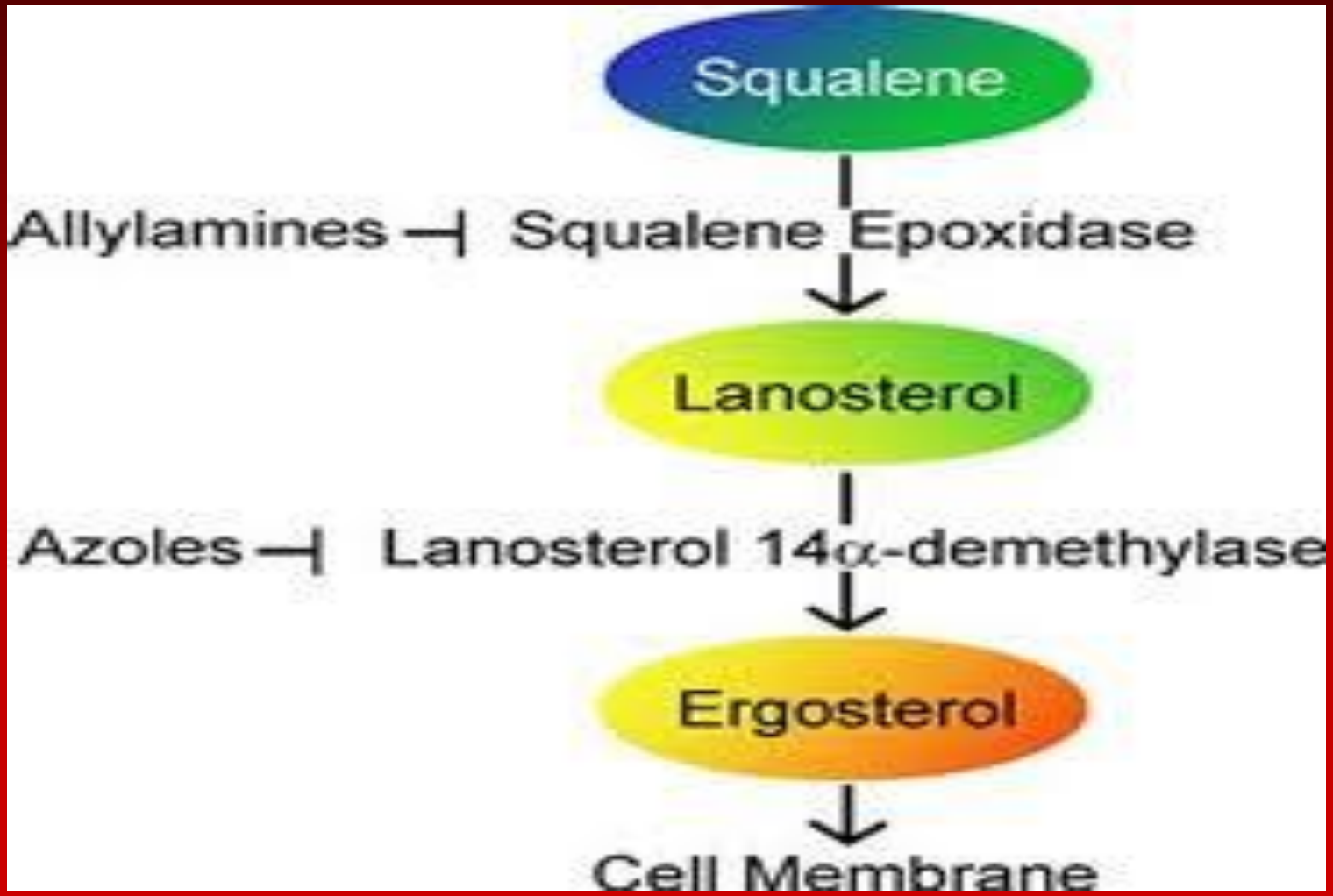
- The name Polyene is derived from their highly *double-bonded* structure. *Amphotericin B* is described as the *prototype*.

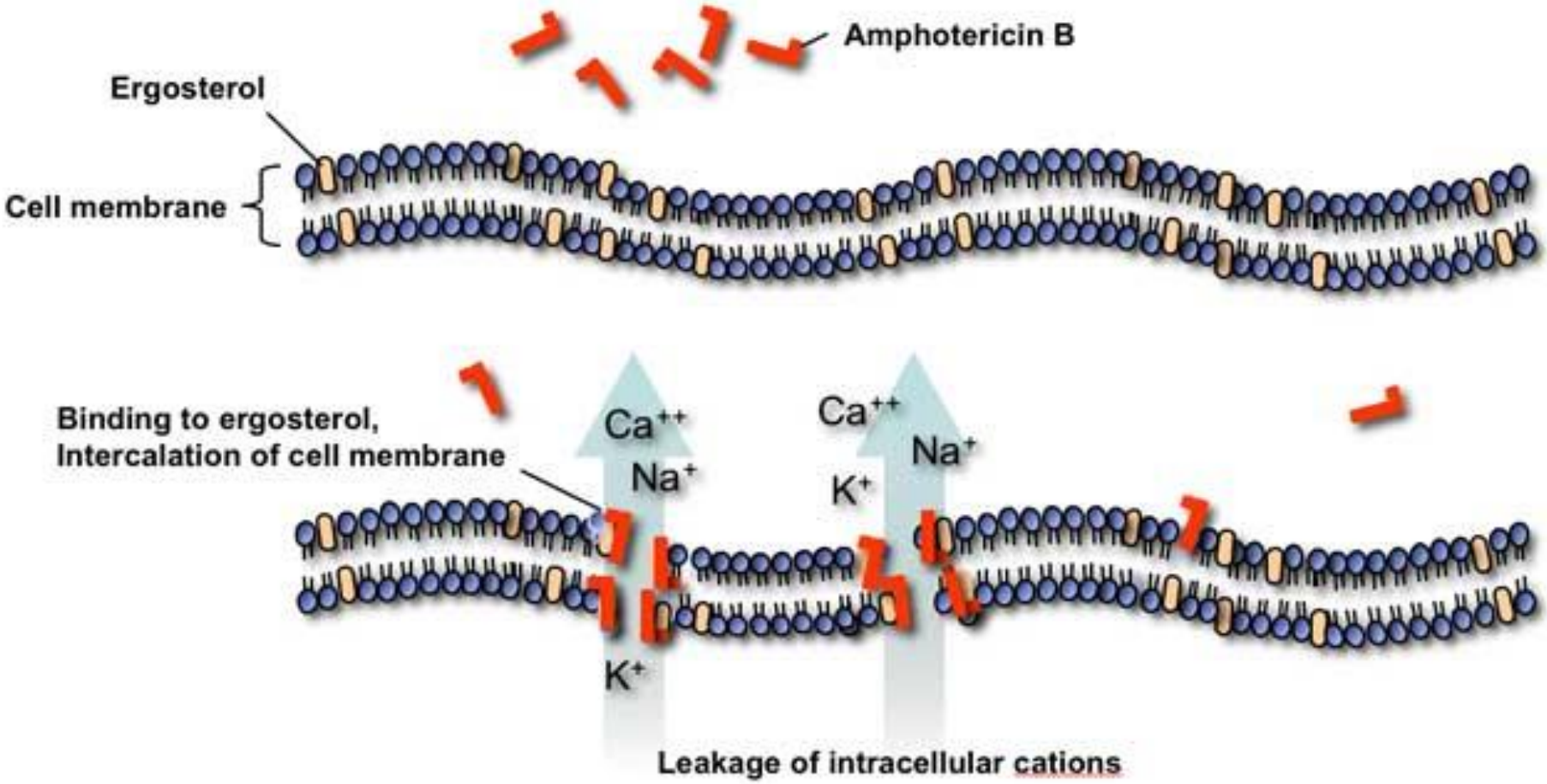


Amphotericin B

Polyene antimycotics, sometimes referred to as **polyene antibiotics**, are a class of antimicrobial polyene compounds that target fungi. These polyene antimycotics are typically obtained from some species of *Streptomyces* bacteria. The polyenes bind to ergosterol in the fungal cell membrane and thus weakens it, causing leakage of K+ and Na+ ions, which may contribute to fungal cell death. Amphotericin B, nystatin, and natamycin are examples of polyene antimycotics.

Amphotericin B (AMB)




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

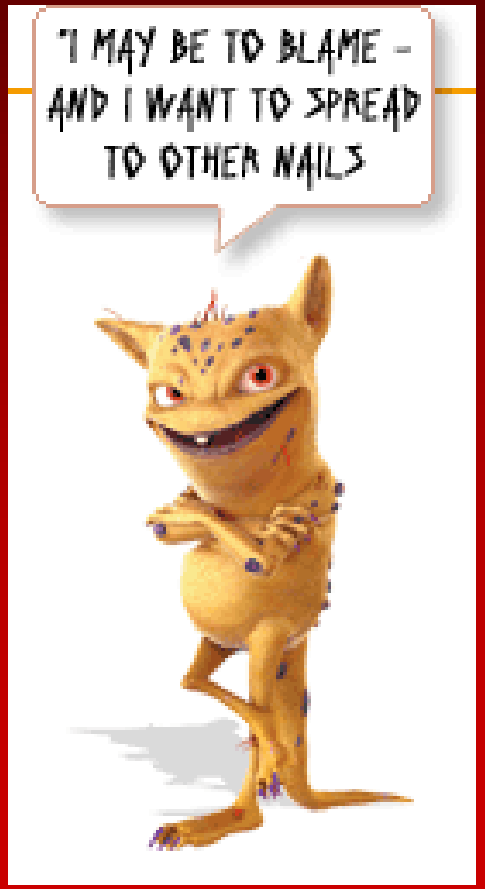
- **AmphotericinB (Fungilin, Fungizone, Abelcet, AmBisome, Fungisome, Amphocil, Amphotec)** is an antifungal drug often used intravenously for systemic fungal infections.

- It is the only effective treatment for some fungal infections.

- Common side effects may include: a reaction which may include fever, headaches and low blood pressure among other symptoms rapidly after it is given, and kidney problems.
- Allergic symptoms including anaphylaxis may occur.

Antifungal Agents

- **Allylamines**
- Allylamines inhibit the enzyme squalene epoxidase, another enzyme required for ergosterol synthesis:
- **Terbinafine - marketed as Lamisil**
- **Amorolfine**
- **Naftifine**
- **Butenafine**



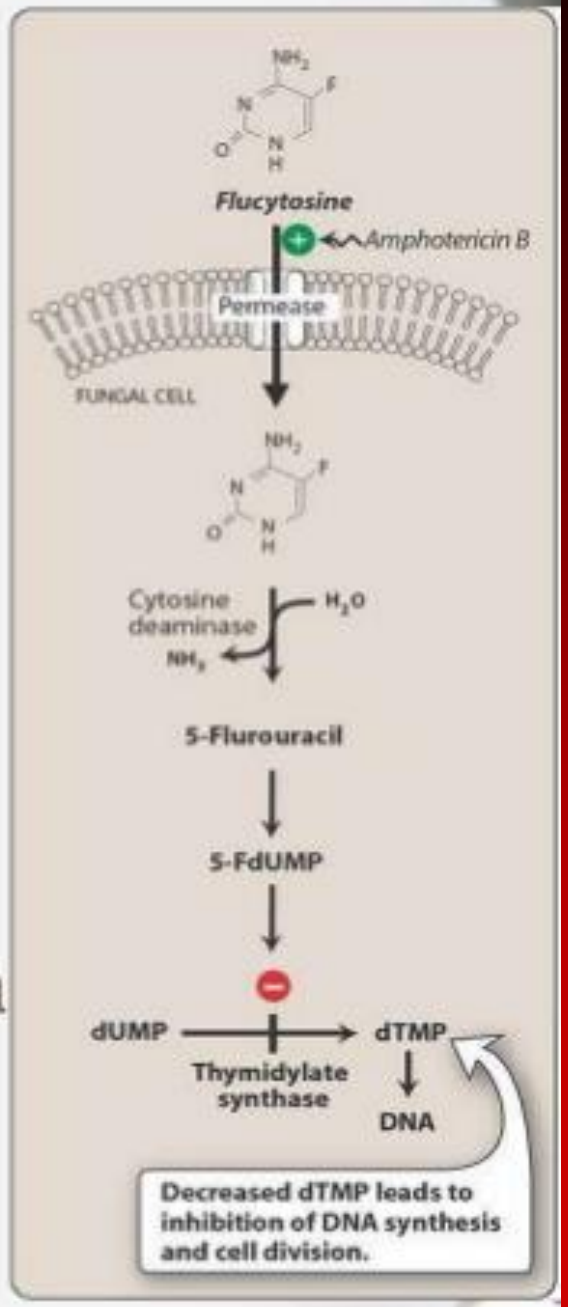
- **Echinocandin**
- Echinocandins inhibit the synthesis of glucan in the cell wall, probably via the enzyme 1,3-β glucan synthase:
  - **Anidulafungin**
  - **Caspofungin**
  - **Micafungin**

Antifungal Agents

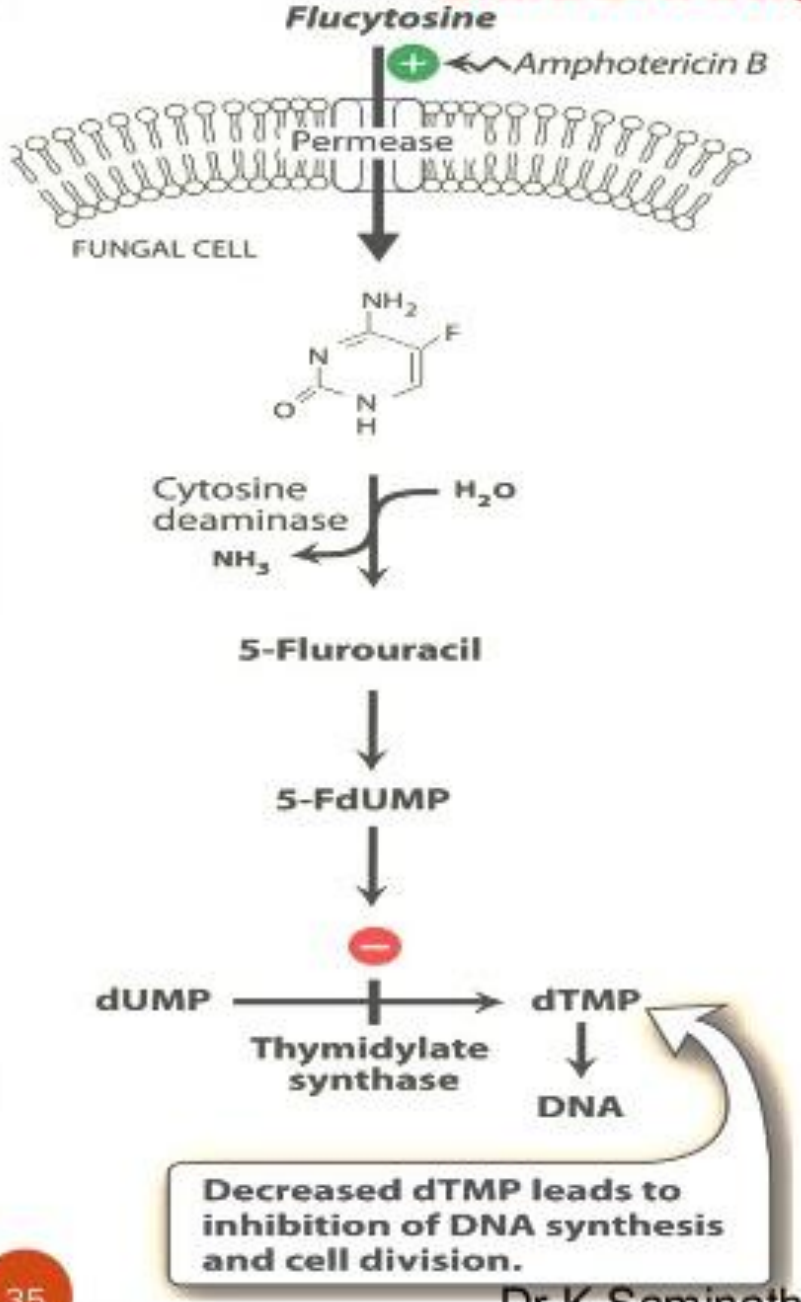
- **Others:**
  - Flucytosine is an antimetabolite.
  - Griseofulvin binds to polymerized microtubules and inhibits fungal mitosis; It is derived from the mold *Penicillium griseofulvum*.
  - Fluocinonide
  - Salicylic Acid (topical)
  - Tinactin or Tolnaftate
  - Potassium Iodide

Flucytosine (5-FC)

- Synthetic pyrimidine, used in combination with **amphotericin B**
- **Amphotericin B** increases cell permeability
- 5-FC forms false nucleotide
- Disrupts nucleic acid and protein synthesis
- Bone marrow depression, dyspepsia hepatic dysfunction



9.MECHANISM OF FLUCYTOSINE



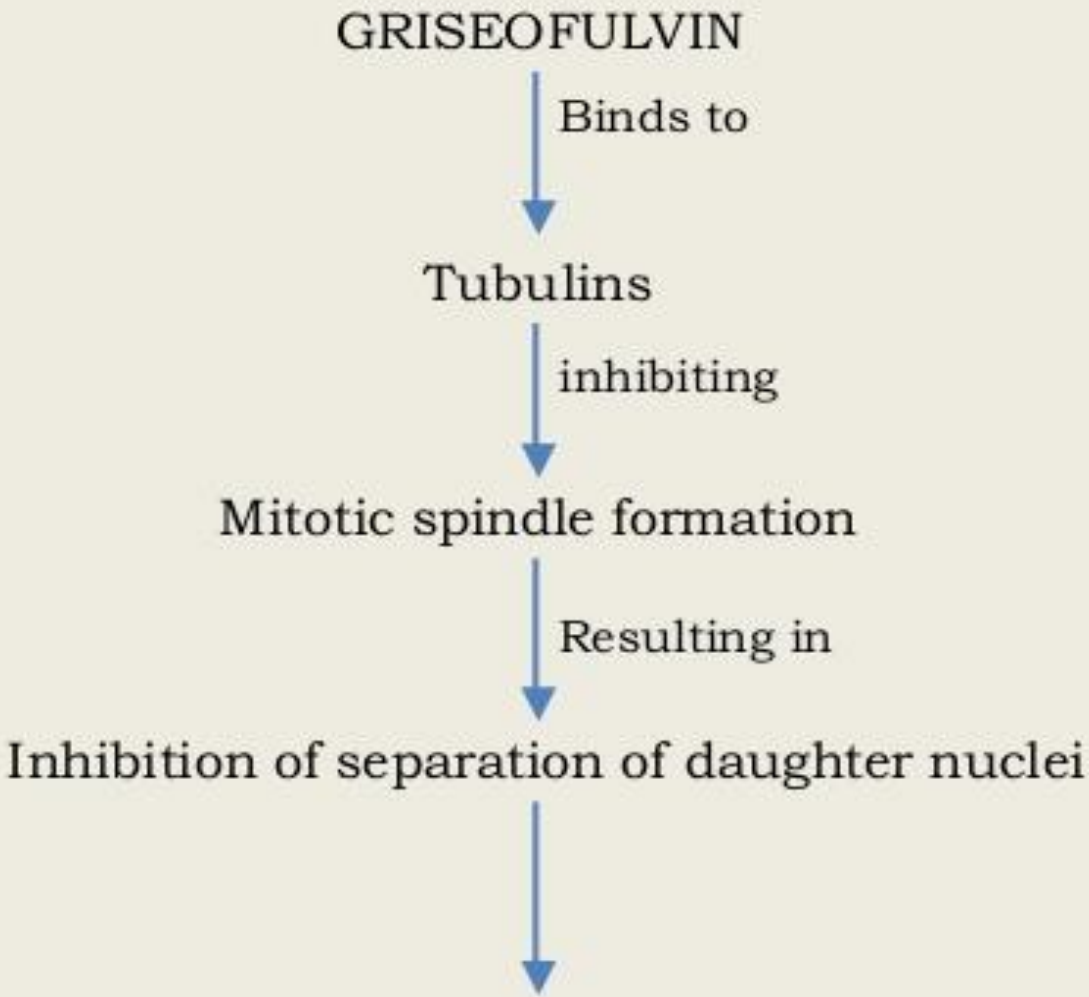
Flucytosine enters fungal cells via a cytosine-specific permeaseâ an enzyme not found in mammalian cells.

Flucytosine is then converted by a series of steps to 5-fluorodeoxyuridine 5'-monophosphate.

This false nucleotide **inhibits thymidylate synthase, thus depriving the organism of thymidylic acid an essential DNA component.**

Note: [Amphotericin B increases cell permeability, allowing more 5-FC to penetrate the cell. Thus, 5-FC and amphotericin B are synergistic.]

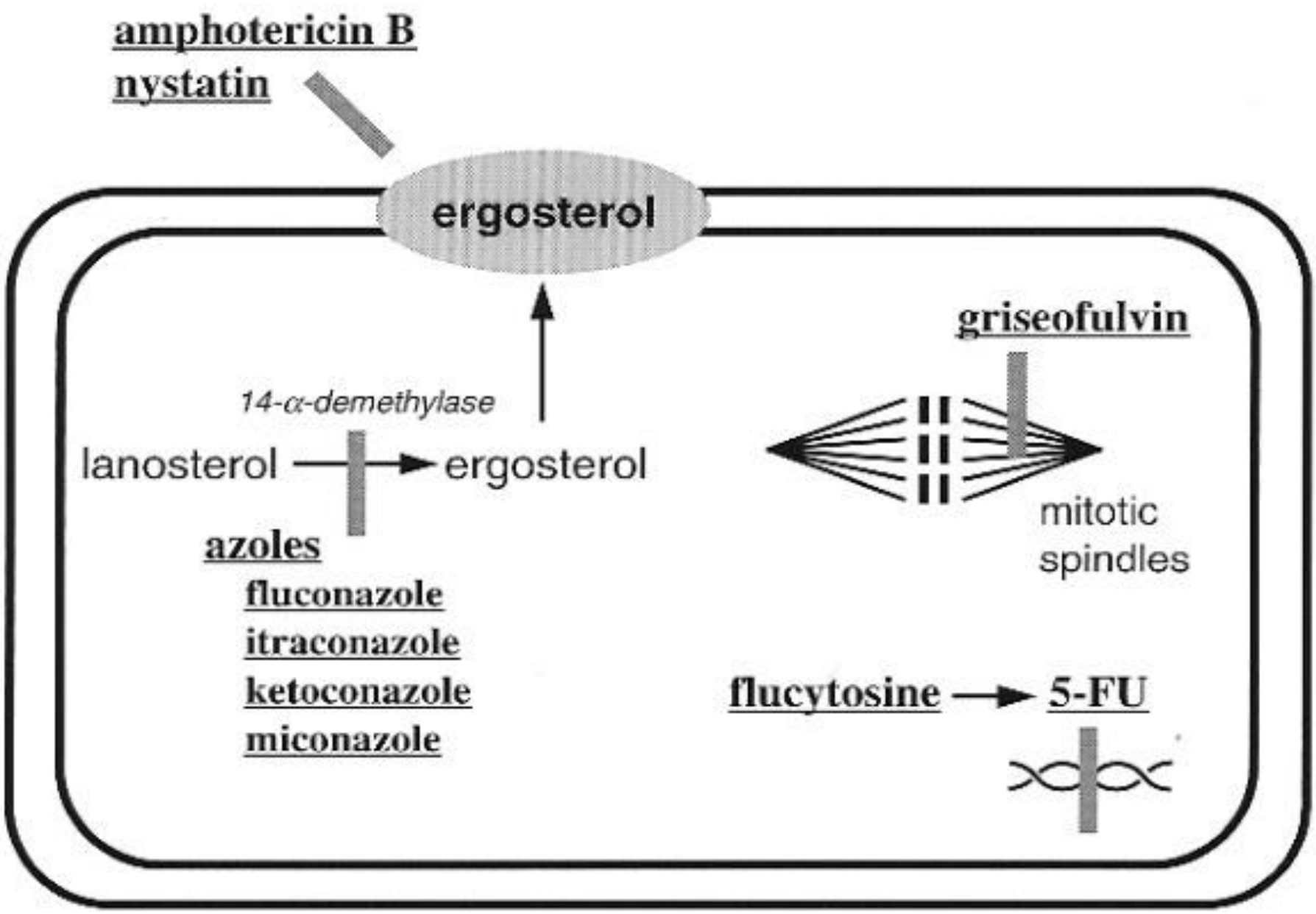
MECHANISM OF ACTION

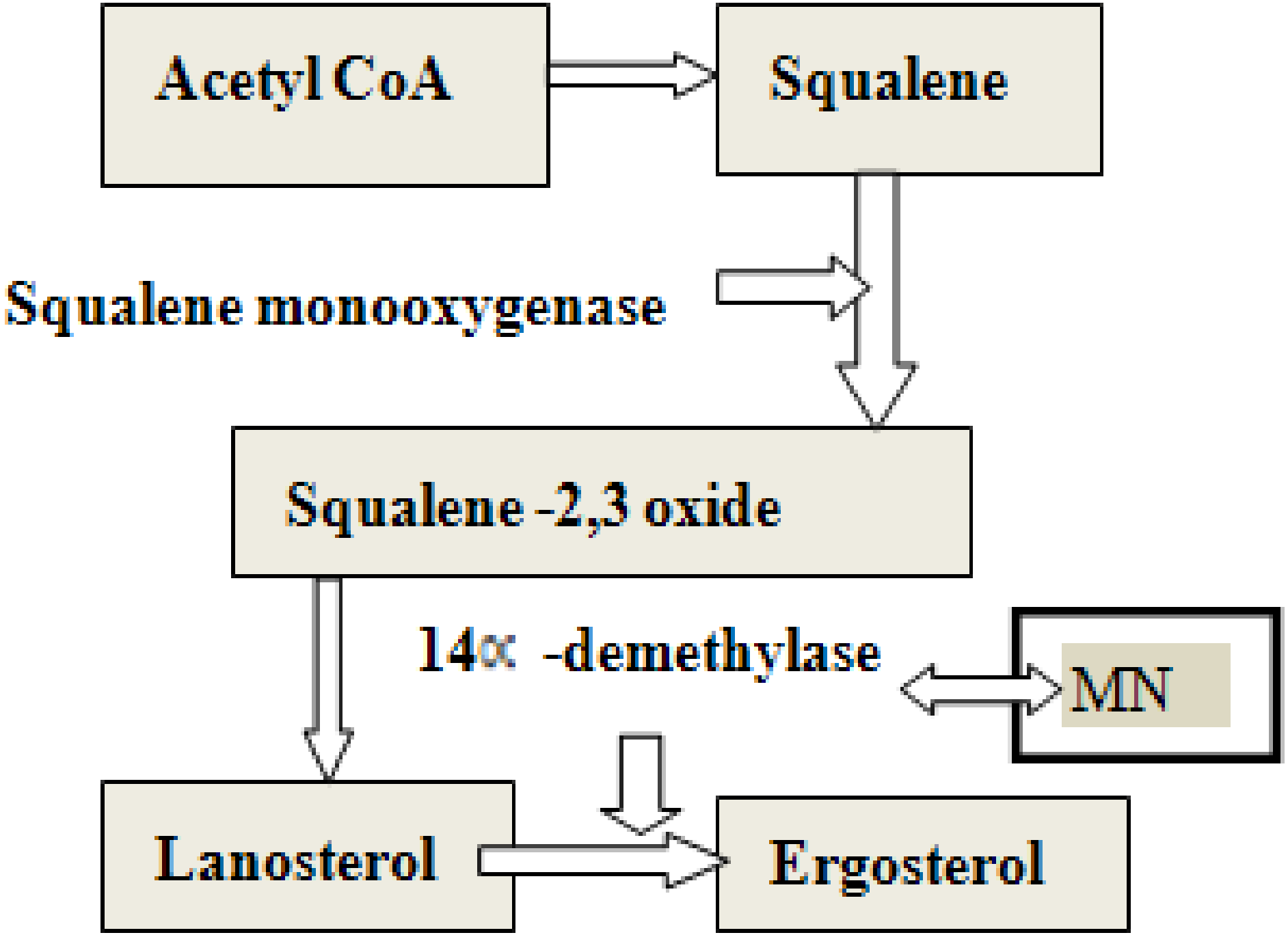


Griseofulvin

- **Mechanism of action :**
- Mechanism of action binds to microtubules comprising the spindles and inhibits mitosis. incorporates into keratin and protects newly formed skin.

Antifungals




Acetyl CoA
Squalene
Squalene monooxygenase
Squalene -2,3 oxide
14α -demethylase
MN
Lanosterol
Ergosterol