ANTITUBERCULAR DRUGS

Points to be covered in this topic

1. INTRODUCTION OF TUBERCULARCULOSIS
2. CLASSIFICATION OF ANTITUBERCULAR AGENTS
3. MOA,PHARMACOKINETICS ,ADR,USES OF DIFFERENT CLASS OF DRUGS
4. TREATMENT OF TUBERCULOSIS

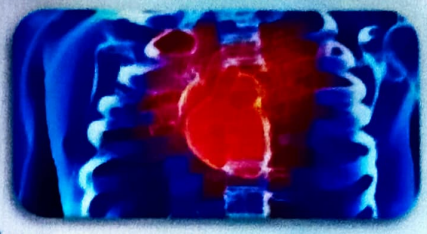
❑ INTRODUCTION

- Tuberculosis (TB) is a **chronic granulomatous** disease caused by ***Mycobacterium tuberculosis*** an **acid-fast bacillus (AFB).**
- Mycobacterial infections require **prolonged treatment.**
- Antitubercular medications are a group of drugs **used to treat tuberculosis.**

❖ Causes

- Tuberculosis is caused by **bacteria that spread** from **person to person** through **microscopic droplets** released **into the air.**
- This can happen when someone with the untreated, active form of tuberculosis **coughs, speaks, sneezes, spits, laughs or sings.**

❖ **Signs and symptoms of tuberculosis**



- Coughing for three or more weeks
- Coughing up blood or mucus
- Chest pain, or pain with breathing or coughing
- Unintentional weight loss
- Fatigue, Fever, Night sweats, Chills

❑ ANTI-TUBERCULAR AGENTS

Antitubercular agents are a group of drugs used to treat tuberculosis.

❑ CLASSIFICATION OF ANTITUBERCULAR AGENTS

S.NO	CLASS	DRUGS
I	FIRST LINE DRUGS	Isoniazid (H) Rifampin (R) Pyrazinamide (Z) Ethambutol (E) Streptomycin (S)
II	SECOND LINE DRUGS	
1	Fluroquinolones	Ofloxacin Levofloxacin Moxifloxacin Ciprofloxacin
2.	Other oral drugs	Ethionamide Prothionamide Cycloserin Terizidone Para amino salicyclic acid Rifabutin Rifapentine
3	Injectable drugs	Kanamycin Amikacin Capreomycin

- **First line :** These drugs have **high antitubercular efficacy** as well as **low toxicity**; are used routinely.
- **Second line :** These drugs have either **low antitubercular efficacy** or **higher toxicity** or both; and are used when first line drugs n cannot be used, or to supplement them.

Alternative groups of Antitubercular drugs

GROUP	DRUGS
GROUP I FIRST LINE ORAL DRUG	Isoniazid (H) Rifampin (R) Pyrazinamide (Z) Ethambutol (E)
GROUP II INJECTABLE DRUGS	Streptomycin (S) Kanamycin Amikacin Capreomycin
GROUP III FLUOROQUINOLONES	Ofloxacin Levofloxacin Moxifloxacin Ciprofloxacin
GROUP IV	Ethionamide Prothionamide Cycloserin Terizidone Para amino salicyclic acid Rifabutin Rifapentine
GROUP V UNCLEAR EFFICACY DRUGS	Bedaquiline Clarithromycin Clifazimine Linezolid Coamoxiclav Imipenem /cilastin

➢ **Adopted from: Treatment of tuberculosis guidelines; WHO (2010) and RNTCP: Technical and operational guidelines for tuberculosis control (2016)**

- **Group I :** are the **most potent** and best tolerated **oral drugs** used routinely.
- **Group II :** are potent and **bactericidal** , but **injectable drugs**.
- **Group III :** includes fluoroquinolones (FQs) which are well tolerated **bactericidal oral drugs**; all patients with drug resistant TB should receive one FQ.
- **Group IV :** are **less effective, bacteriostatic/more toxic oral drugs** for **resistant TB**.
- **Group V :** are drugs with uncertain efficacy; not recommended for **MDR-TB**; may be used as reserve drugs, and in extensively resistant TB (XDR-TB).

FIRST LINE DRUGS

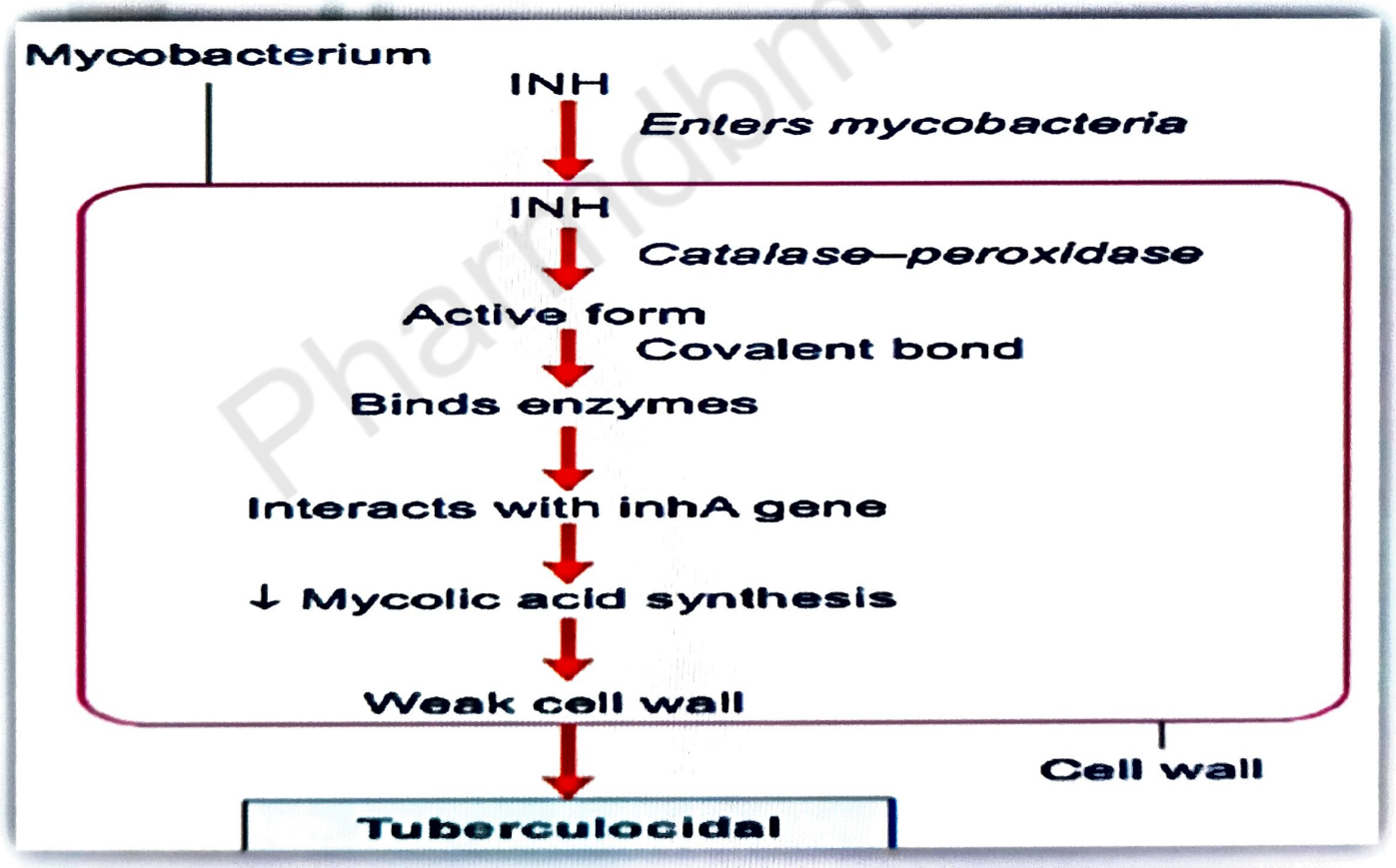
Isoniazid (H) , Rifampin (R),Pyrazinamide (Z),Ethambutol (E), Streptomycin (S)

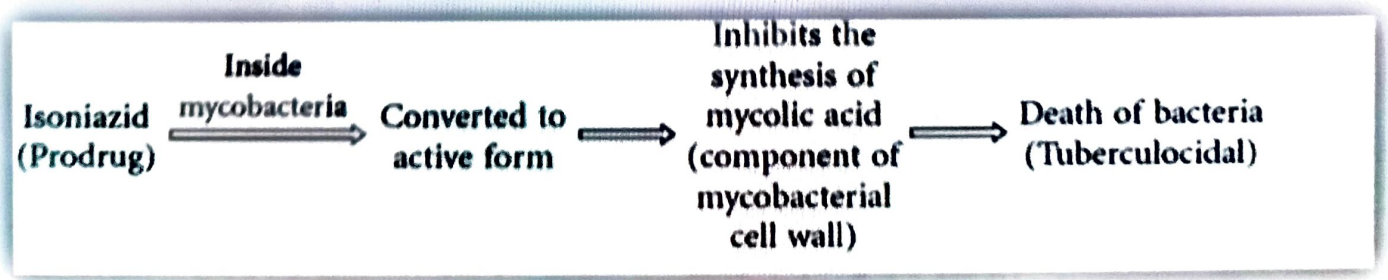
i. Isoniazid (H)

- Isoniazid is a **highly effective** and the most widely used **antitubercular** agent.
- It is **orally effective, cheapest** and has **tuberculocidal activity.**
- It is **active against both intracellular and extracellular bacilli.**
- It is a first-line drug for the **treatment of tuberculosis.**
- It is also used for **chemoprophylaxis of tuberculosis**

❖ Mechanism of action

- Isoniazid **inhibits the biosynthesis of mycolic acids**, which are essential constituents of the **mycobacterial cell wall.**
- INHinhibits the **synthesis of mycolic acids** which are important components of the mycobacterial cell wall.
- The cell wall of mycobacteria differs from other bacteria in having large **amounts of mycolic acids** which form essential components of mycobacterial cell wall. INH, a prodrug, freely **enters the mycobacteria and is converted to an active form by an enzyme catalase-peroxidase (Kat G) present in the mycobacteria.**
- This active form covalently binds certain enzymes and thereby **inhibits mycolic acid synthesis.**



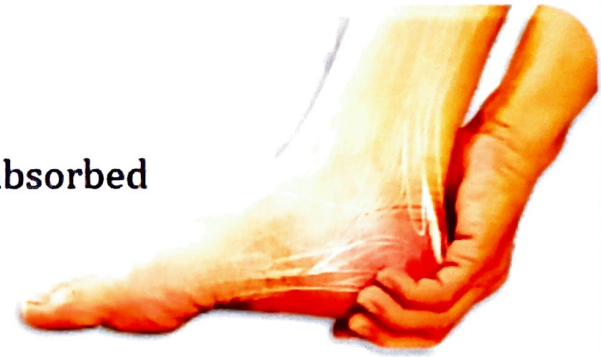


❖ **Resistance** to INHis seen when there is over **production of the enzymes** that are **inhibited by INH**. **Mutations of *INH A* and *Kat G* enzymes** also result in resistance.

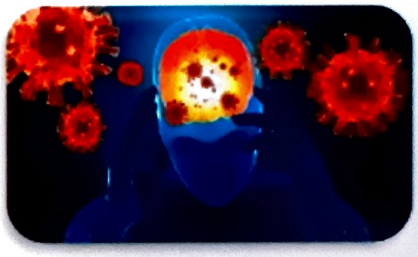
❖ Pharmacokinetics

- INHis completely **absorbed orally and penetrates** all body tissues, **tubercular cavities, placenta and meninges.**
- It is extensively metabolized in liver, most important pathway being **N-acetylation by NAT2.**
- The **acetylated metabolite is excreted in urine.**
- The rate of **acetylation of INH**is under genetic control resulting in either rapid or slow acetylators .
- It **Cross placenta barrier.**

❖ Adverse effect



- Pulmonologist—peripheral neuritis
- Cleverly—CNS toxicity; Completely absorbed
- Prevented—pyridoxine
- INH
- Mycolic acid synth inhibition
- Intra- and extracellular organisms
- Seizures
- Hepatitis, hepatotoxicity
- Acetylation—fast and slow
- Psychosis



✓ Mnemonic on INH

- **Pulmonologist Cleverly Prevented INHMISHAP**

❖ Interaction

Isoniazid inhibits the metabolism of phenytoin , carbamazepine, warfarin , increases the plasma levels of these drugs may result in **toxicity.**

❖ Uses

- Isoniazid (INH) is a **first-line drug** for the **treatment of TB.**
- It is also used for **chemoprophylaxis of TB**

ii. Rifampin (R)

- It is a **semisynthetic derivative of Rifamycin B** obtained from **Streptomyces mediterranei .**
- Rifampin is **bactericidal** to ***M. tuberculosis*** and many other **gram-positive and gram-negative bacteria like *Staph. aureus, N. meningitidis, H. influenzae, E. coli, Klebsiella, Pseudomonas, Proteus* and *Legionella.***
- Rifampin is a derivative of **rifamycin** and is a first-line antitubercular drug.
- It **rapidly kills intracellular and extracellular bacilli** including spurters
- Rifampin is called **sterilizing agent.**

❖ Mechanism of action

- Rifampin **binds to bacterial DNA-dependent RNA polymerase** and **inhibits RNA synthesis.**
- It has **bactericidal** effect against mycobacteria, **N. meningitidis, H. influenzae, S. aureus, E. coli, Pseudomonas, etc.**

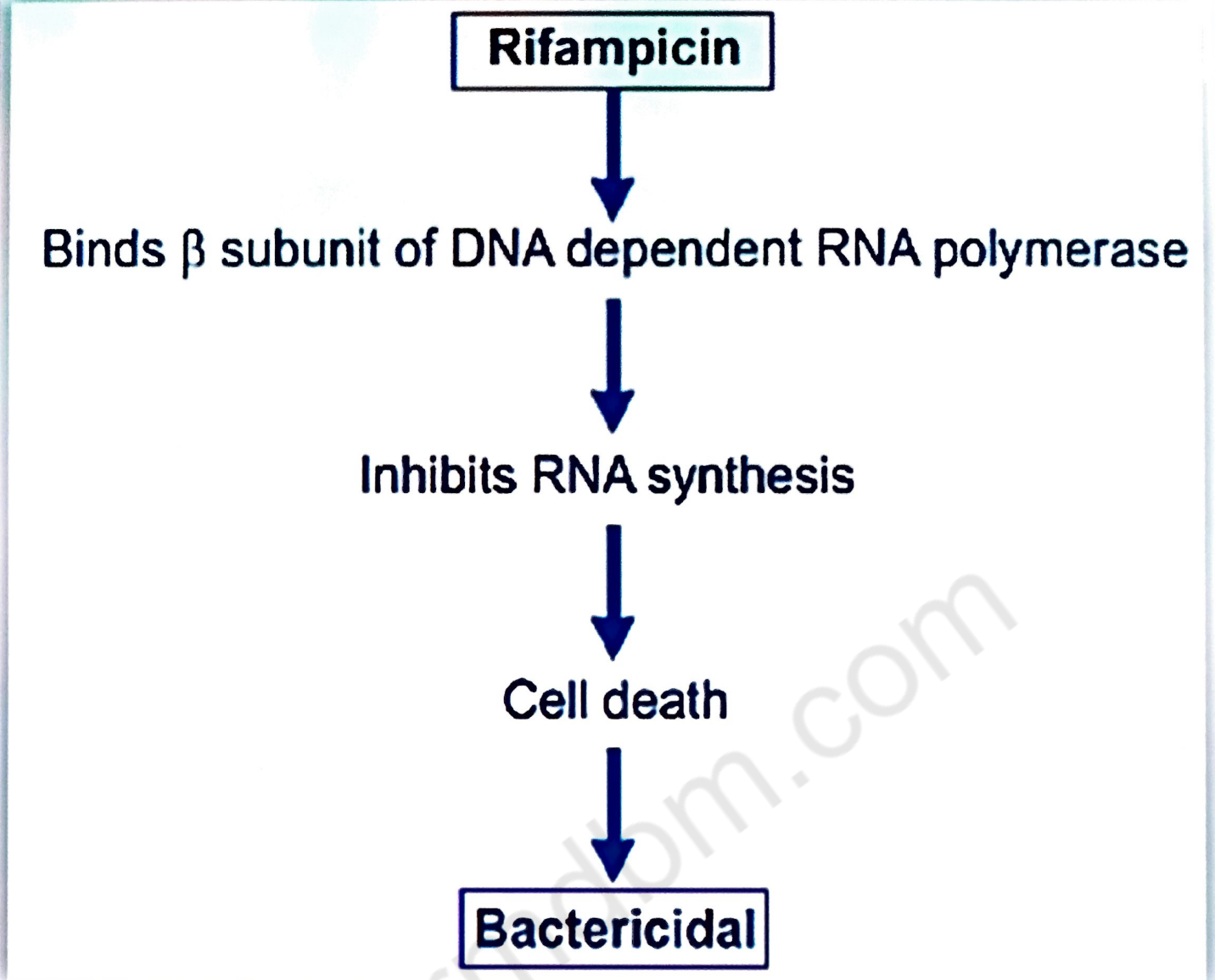
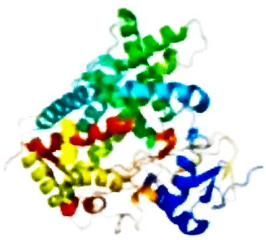


Fig:- Mechanism of action of rifampicin

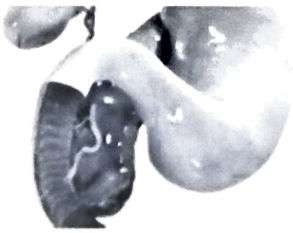
❖ Interaction

- Rifampin is a microsomal enzyme inducer—increases several **CYP450** isoenzymes, including **CYP3A4, CYP2D6, CYP1A2** and **CYP2C** subfamily.
- Drugs including **warfarin, oral contraceptives, corticosteroids, sulfonylureas, HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors theophylline, metoprolol, fluconazole, ketoconazole, clarithromycin, phenytoin.**



❖ Pharmacokinetics

- It is given **orally and is rapidly absorbed from the GI tract**, but presence of food **reduces its absorption;**
- It is distributed widely throughout the body and gets **metabolized in liver.**
- The active **deacetylated form** is **excreted in bile** and undergoes **enterohepatic recycling.**
- The rest of the **drug is excreted in urine.**



❖ Adverse effects

- **Hepatitis** is the main adverse effect—the risk of **hepatotoxicity** is more in alcoholics and elderly patients.
- **Flu-like syndrome** with **fever, chills, headache, muscle and joint pain.**
- **GI disturbances** such as **nausea, vomiting and abdominal discomfort.**
- Skin rashes, itching and flushing.

Rifampicin Important Points

R : RNA Polymerase Inhibitor , Reddish orange discoloration

I : Interstitial nephritis

F : Flu like symptoms

A : Anaemia

M : Maximum cidal and sterilizing effect

P: Platelet count decreases

I: Inducer of enzyme

C: Contraceptive failure

I: INR deranged with warfarin

N: NNRTI and PI failure

❖ Uses

i. **Tuberculosis**

ii. **Leprosy**

iii. **Prophylaxis of meningococcal and H. influenzae meningitis**

iv. Rifampin in combination with – **β lactam antibiotics** may be useful in **staphylococcal infections** such as **endocarditis, osteomyelitis**, etc.

v. Rifampin is used with **doxycycline** for the treatment of **brucellosis.**

iii. Pyrazinamide (Z)

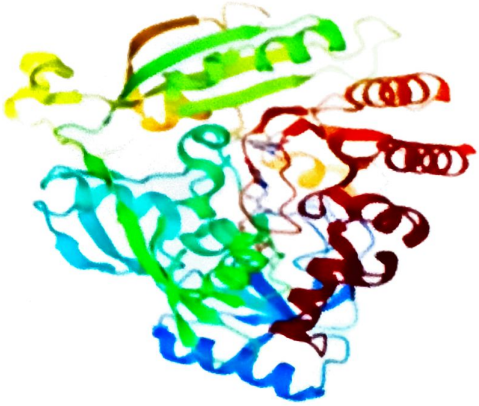
- Pyrazinamide is a **synthetic analogue of nicotinamide.**
- It is active in **acidic pH**—effective against **intracellular bacilli** (has sterilizing activity).
- It has **tuberculocidal activity**. Like **INH.**

❖ Mechanism of action

- Pyrazinamide **inhibits mycobacterial mycolic acid biosynthesis** but by a different mechanism.
- Pyrazinamide is a **prodrug** that is activated by **mycobacterial pyrazinaminidase into pyrazinoic acid,** which **inhibits fatty acid synthetase I** and this **inhibits mycolic acid synthesis.**
- Pyrazinamide is active in acidic environment present inside the **phagocytes and granulomas** and hence is effective **against intracellular, slow growing organisms..**

❖ Resistance

Mutation in **pyrazinaminidase gene (pnca)** which makes **pyrazinaminidase** that **does not activate pyrazinamide.**



❖ Pharmacokinetics

- It is given **orally**, **absorbed well** from **GI tract** and is distributed widely throughout the **body including the CSF**.
- It is **metabolized in liver** and **excreted in urine.**

❖ Adverse effect

- **Hepatotoxicity**
- **Hyperuricaemia**
- **Acute attacks of gout**
- **Flushing arthralgia**

❖ **Side effects** are **anorexia, nausea, vomiting, fever and skin rashes.**

❖ **Uses** :- Pyrazinamide is a medication used **to treat tuberculosis.**

iv. Ethambutol (E)

- It is a first-line **antitubercular drug.**

❖ Mechanism of Action

- **Arabinosyl transferase** in **mycobacterium synthesizes arabinogalactan** and **lipoarabinomannan,** which are integral component of cell wall.
- **Ethambutol inhibits cell wall synthesis by inhibiting arabinosyl transferase.**

❖ **Resistance** can be seen by mutation in **arabinosyl transferase(embB) gene.**

❖ Pharmacokinetics

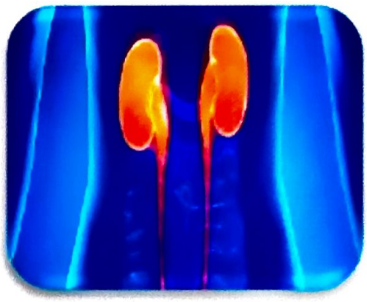
- Ethambutol is **well absorbed after oral administration**, distributed widely in the body.
- It is **metabolized in liver**, **crosses BBB in meningitis** and **excreted in urine.**

❖ Side Effects

- **Optic neuritis** and **red-green colour blindness (green > red)** that is why it is avoided in children.
- Vitamin B-12 supplementation might **decrease severity of ocular toxicity.**
- **Hyperuricemia**
- Ethambutol is **excreted by kidney**, its dose should be **decreased in renal failure.**
- **Nausea, vomiting, abdominal pain, skin rashes, itching** and **joint pain.**

❖ Uses

- Ethambutol is a **static drug effective** against only **extracellular mycobacterium.**
- It is the **least potent drug of all in first-line**.
- It is used for treatment of **TB** in **continuous phase, MAC and mycobacterium kanasii infection.**



V. Streptomycin (S)

- Streptomycin is an **aminoglycoside antibiotic**.
- It is a **bactericidal drug**.
- It is **active against extracellular bacilli in alkaline pH.**
- Streptomycin is **not effective orally;** it must be **injected intramuscularly.**

❖ Adverse effects

- **Ototoxicity ,Nephrotoxicity ,Neuromuscular blockade**

❖ **Uses** to treat infections **(such as *Mycobacterium avium* complex-MAC, tularemia, endocarditis, plague)** along with other medications.

SECOND LINE DRUGS

- The second-line drugs are reserved for **treatment of drug resistant tuberculosis.**
- **Multidrug resistant (MDR) TB** is a case of TB that is resistant to both **isoniazid and rifampicin.**
- Extremely drug resistant (XDR) TB is a case of MDR with additional resistance to a fluoroquinolones and to at least one of the injectable **second-line drugs** like **Amikacin , kanamycin or Capreomycin .**

1. FLUOROQUINOLONES (FQS)

Ofloxacin, Levofloxacin , Moxifloxacin ,Ciprofloxacin

- **Fluoroquinolones (fqs) like ofloxacin (ofx),, levofloxacin (lfx), ciprofloxacin (cfx) and moxifloxacin (mfx)** are relatively new potent oral **bactericidal drugs for TB**, that have gained prominence as well tolerated **second line anti-TB drugs.**
- **Fluoroquinolones inhibit tubercle bacilli** as well as **atypical mycobacteria** in addition to **gram-positive and gram-negative bacteria.**
- They are **active against MAC, *M. fortuitum* .**
- They enter into the cells and destroy intracellular mycobacteria. **Levofloxacin** and **Moxifloxacin** are the FQs used in tuberculosis resistant to first-line drugs.
- Fluoroquinolones have been used along with second-line drugs in **multidrug-resistant TB.**
- **Moxifloxacin** is the most active **FQ against *M.tuberculosis.***
- **Ciprofloxacin, is more active than levofloxacin** against atypical mycobacteria, but is not used for ***M. tuberculosis* now.**

- The **Fluoroquinolones penetrate cells** and **kill mycobacteria** lodged inside **macrophages as well.**
- **Ciprofloxacin, moxifloxacin** and **levofloxacin— bactericidal agents**, given **orally.**

Dose : Ofloxacin 800 mg OD

Levofloxacin 1000 mg OD For > 45 kg

Moxifloxacin 400 mg OD body weight

2 . ORAL DRUGS

Ethionamide ,Prothionamide ,Cycloserin , Terizidone ,Para amino salicyclic acid (PAS) ,Rifabutin , Rifapentine

i . Ethionamide & Prothionamide

- It is introduced in **1956**, which acts on **both extra- and intracellular bacilli.**

❖ Mechanism of action

- Ethionamide **inhibits acyl protein carrier reductase (INH A)** and hence **inhibits mycolic acid synthesis.**
- Because of same reason INH A gene over expression confers cross resistance of isoniazid to ethionamide.
- It is a bacteriostatic drug.

❖ Adverse effects

- **Anorexia**
- **nausea**
- **Vomiting and epigastric pain**
- **Salivation**

❖ **Resistance** to Ethionamide mostly results from **mutation of the gene** that encodes for the **Ethionamide activating enzyme**.

❖ **Pharmacokinetics**

- It is completely absorbed **orally**, distributed all over and **crosses into CSF.**
- It is completely metabolized in **liver** and has a **short t½ of 2–3 hours**.

❖ **Side effects** are **hepatitis, headache, blurred vision** and **paraesthesia .**

✓ **Mnemonics**

❖ **Adverse effects of Ethionamide**

E : Elevated ALT/AST

T : Taste change (metallic)

H : Hypothyroidism

I : Impotence

O : Ocular toxicity

N : Nausea and vomiting

❖ **Uses**

- Ethionamide is used only for **drug-resistant TB.**
- It is a component of the **RNTCP standardized regimen for MDR-TB** and an optional drug for inclusion into the treatment regimen of **MAC infection in AIDS patients.**
- It is also a **reserve drug for leprosy**.

ii . Cycloserin (Cs)

This antibiotic obtained from **S.orchidaceus** is an analogue of **D-alanine.**

❖ Mechanism of action

- **Inhibits bacterial cell well synthesis** by **inactivating the enzymes** which **racemize l-alanine** and link **two d-alanine** residues
- **Cycloserin** is an antibiotic that inhibits cell wall synthesis, is tuberculostatic .
- It is effective against some gram +ve organisms , *E.coli* and *Chlamydia*.

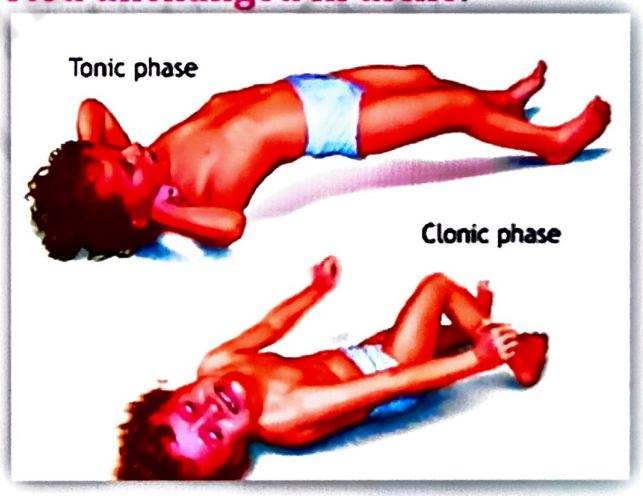
❖ Resistance to Cs develops slowly; no cross resistance with any other anti-TB drugs occurs.

❖ Pharmacokinetics

- Oral absorption of Cycloserin is **good,** it diffuses **all over the body.**
- It is **metabolized in liver** & **excreted unchanged in urine.**

❖ Adverse effects

- **Headache, tremors**
- **Psychosis**
- **Seizures. Sleepiness**
- **Slurring of speech**
- **Depression or frank psychosis**



❖ Uses

- Resistant tuberculosis especially **MDR cases.**
- It is included in the **standardized regimen** used by **RNTCP for MDR-TB.**

iii. Terizidone

- Mechanism of action & antibacterial properties is similar to Cycloserine

iv. Para amino salicyclic acid (PAS)

- Introduced in **1946**
- It is structurally similar to **sulphonamides.**

❖ Mechanism of action

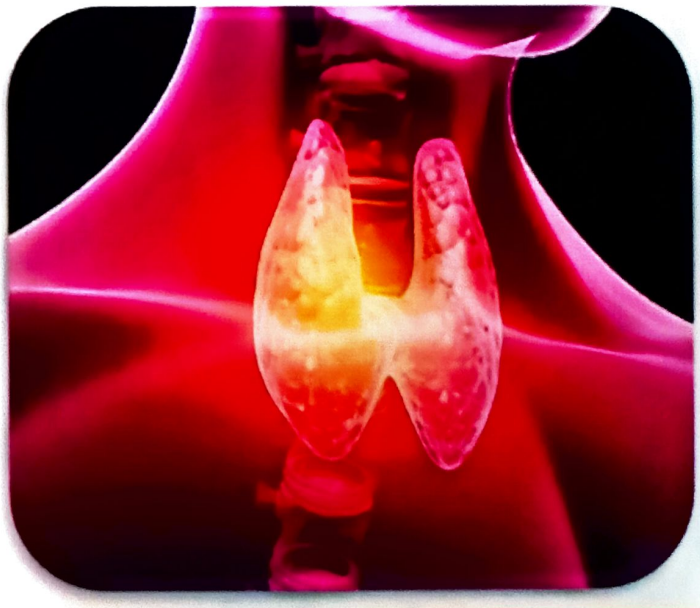
- PAS also competitively **inhibits folate synthetase enzyme** and **produces tuberculostatic effect.**
- At present, PAS is a reserve drug for the management of **MDR-tuberculosis.**

❖ Pharmacokinetic

- PAS is **absorbed completely by the oral route**
- Distributed all over **except in CSF.**
- About 50% para amino salicyclic acid is **acetylated,** competes with acetylation of INH And prolongs its t½.
- It is excreted rapidly by **glomerular filtration** and **tubular secretion.**

❖ Adverse effect

- **Anorexia**
- **Nausea**
- **Epigastric pain**
- **Rashes**
- **Fever**
- **Malaise**
- **Hypokalaemia**
- **Goiter, liver dysfunction**
- **And rarely blood dyscrasias**



❖ Uses

- PAS is used only in **resistant TB**

v. Rifabutin

- It is related to rifampin in structure and mechanism of action, but is **less active** against **M.tuberculosis**.
- It is **more active against MAC**. Majority of **M.tuberculosis** isolates resistant to R are cross resistant to rifabutin.
- It is **not** an option for **treatment of MDR-TB.**

❖ Pharmacokinetic

- Oral bioavailability of rifabutin is low

❖ Adverse effect

- **Gastrointestinal intolerance**
- **Rashes**
- **Granulocytopenia**
- **Myalgia and uveitis**

❖ Uses

- The **dose of rifabutin needs to be reduced** when it is **used to treat TB** in a **HIV patient** receiving a **protease inhibitor**.
- The primary indication of rifabutin is for **prophylaxis** and treatment of **MAC infection in HIV-AIDS patients.**
- Rifabutin is also used for the **treatment of MAC infection** in combination with clarithromycin and Ethambutol

vi. Rifapentine

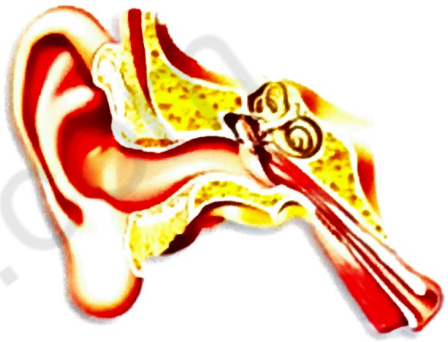
Rifamycins : Rifapentine and **rifabutin—bactericidal agents, given orally**

3. INJECTABLE DRUGS

Kanamycin, Amikacin , Capreomycin

i. Kanamycin

- It is obtained from **S. Kanamyceticus (in 1957).**
- It was the second systemically used aminoglycoside to be developed after streptomycin.
- Kanamycin is similar to **streptomycin** .
- It is Including efficacy **against M. Tuberculosis** and lack of activity on **pseudomonas and streptococci.**



❖ Adverse effect

- **Hearing loss**
- **Vestibular disturbance**
- **Because of toxicity and narrow spectrum of activity**

❖ Uses

- Kanamycin is occasionally used as a second line drug in **resistant tuberculosis.**

ii. Amikacin

- It is a semisynthetic derivative of kanamycin
- Amikacin and kanamycin— **bactericidal agents, administered parenterally.**
- Amikacin is effective **in tuberculosis**, but used only for **multidrug resistant infection.**
- More **hearing loss than vestibular disturbance** occurs in toxicity

iii. Capreomycin

- It is a **cyclic peptide antibiotic**, chemically very different from aminoglycosides, but with similar **mycobactericidal activity,**

❖ Adverse effect

- **Ototoxicity and nephrotoxicity**
- **Eosinophilia**
- **Rashes**
- **Fever**
- **Injection site pain.**
- **It has to be injected I.M.**

❖ Uses

- It is used only as alternative to **aminoglycoside antibiotics**

ALTERNATIVES GROUPS

i. Bedaquiline

- it is introduced **antibacterial is a diarylquinoline**.

❖ Mechanism of action

- It **binds to and inhibits mycobacterial ATP synthase** and thereby interferes with the generation of energy.
- It is tuberculocidal.
- Fatty food increases its **bioavailability,** is extensively bound to plasma proteins and is **metabolized by microsomal enzymes (cytochrome P450).**
- Co-administration of other microsomal enzyme inducers like **rifampicin and also enzyme inhibitors should be avoided.**

❖ Adverse effects

- QTC prolongation
- Hepatotoxicity,
- Nausea, Arthralgia and Headache

❖ Uses

- Treatment of **MDR tuberculosis** in combination with other **antitubercular drugs.**

❑ TREATMENT OF TUBERCULOSIS

❖ BIOLOGY OF TUBERCULAR INFECTION

- Originally **18-24 months (1990)** but now **6 months** short course
- Aerobic organism – un favourable condition remain dormant or intermittently grow – several subpopulation
- **Rapidly growing with high bacillary load**: wall of a cavitary lesion (susceptible to H- less for R, E, S) Slow growing: located intracellularly and at inflamed sites **(susceptible to Z - H, R and E are less active)**
- **Spurters**: within caseous **material - Oxygen tension is low** and **neutral pH (susceptible to R)**
- **Dormant**: totally inactive for prolonged period – No anti-TB drug

❖ SHORT COURSE CHEMOTHERAPY

- WHO short course: **6 - 8 months multidrug short course regimens** (DOTS) 1997 -Implemented in India (WHO)
- "Stop TB" strategy by WHO in 2006 – spread of MDR TB
- 2010 - New Case or previously treated or Drug resistant TB or MDR TB
- 2016 RNTP - Drug sensitivity test for DR-TB= Liquid culture and drug susceptibility test (L-DST) and genotyping tests for resistance to different drugs

1. Intensive phase : The patient receives intensive treatment with four tuberculocidal drugs daily or thrice weekly for a period **2 months**.

- **Intensive phase : INH(H) 300 mg Rifampin (R) 450 mg Pyrazinamide (Z) 1500 mg Ethambutol (E) 800 mg/Streptomycin (S) 1000 mg Pyridoxine 10 mg daily for 2 months.**

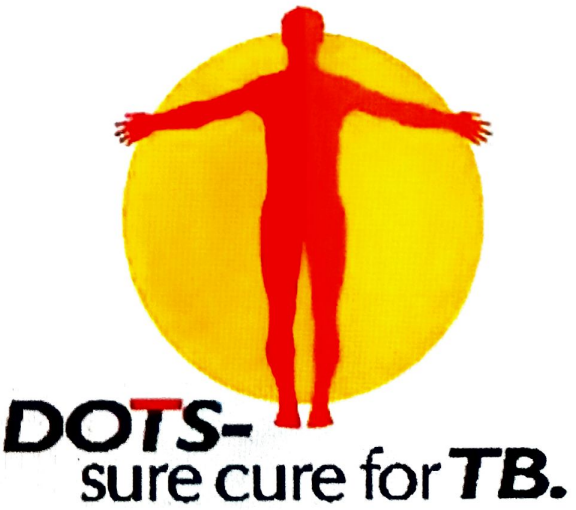
2. Continuation phase : The patient receives two drugs—usually INH And rifampin— **daily or thrice weekly** for a period of **4 months**. This phase helps to eliminate the remaining bacilli and prevents relapse.

- **Continuation phase: INH300 mg Pyridoxine 10 mg Rifampin 450 mg daily for 4 months. Isoniazid, rifampin, pyrazinamide and pyridoxine are administered orally half-an-hour before breakfast.**

Streptomycin is given intramuscularly.

❖ The WHO Guidelines for the Treatment of Tuberculosis

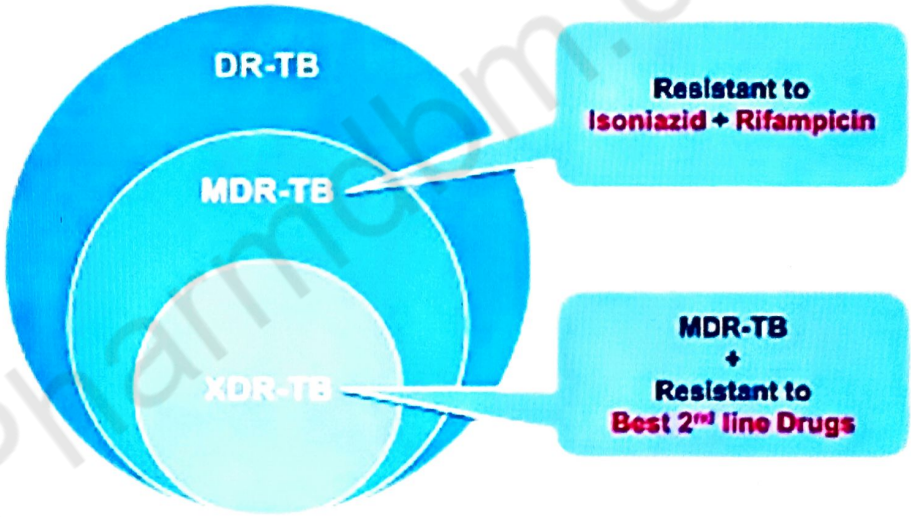
- **Revised National Tuberculosis Control Programme (RNTCP)** was launched in India in **1997**.
- Under this programme, **DOTS (directly observed treatment short course)** chemotherapy is being implemented.
- Out of the WHO-recommended regimens, the **thrice-weekly regimen** is followed in DOTS.
- **DOTS is the backbone of RNTCP.**
- It is aimed at ensuring patient compliance thus preventing the emergence of **drug-resistant tuberculosis.**



- **Specimens for culture and drug susceptibility testing (DST)** should be obtained from all previously treated patients at or before start of treatment

❖ Multidrug-resistant Tuberculosis (MDR-TB)

- It is defined as resistance to **both isoniazid and rifampicin with or without resistance** to any other **anti-TB drugs.**
- MDR-TB can be treated by either specially designed **standardized or individualized regimens.**
- **MDR-TB** should be treated with regimens containing **at least four drugs** to which organisms are known or presumed to be susceptible. Treatment should be given for at least **18–24 months** beyond culture conversion



❖ Extensively Drug-Resistant (XDR) Tuberculosis

- Extensively drug-resistant (XDR) tuberculosis is defined as resistance to **INH, Rifampicin , Fluoroquinolones** and one of **capreomycin/ kanamycin /Amikacin .**

❖ TB Treatment in HIV Patients

- TB treatment is the same for HIV-infected as for non-HIV-infected TB patients. Short-course chemotherapy must be started, once TB is diagnosed.

Rifabutin is preferred over rifampin in HIV patients on antiretroviral drugs such as **protease inhibitors**, as it does not interact with them

❖ Tuberculosis in Pregnancy

- All first-line drugs **(INH, rifampin, pyrazinamide and Ethambutol)** except **streptomycin** can be used in pregnancy.

❖ Chemoprophylaxis of Tuberculosis

- It is the **prophylactic use of antitubercular drugs** to prevent the development of **active tuberculosis.**
- **INH with rifampin** is used for **chemoprophylaxis** as they are orally effective, less toxic and cheap.

➢ Indications for chemoprophylaxis

i. Newborn of a mother with active tuberculosis.

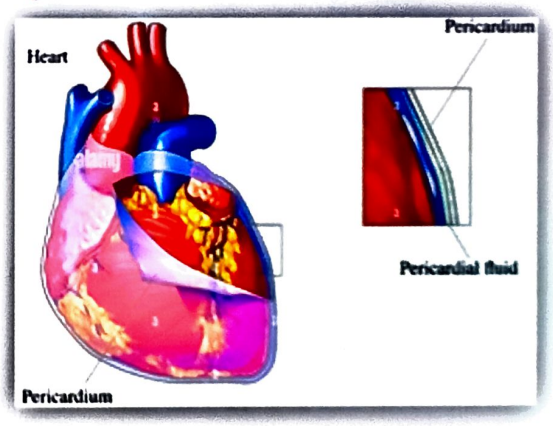
ii. Young children (6 years) with positive tuberculin test.

iii. **Household** contacts of patients with tuberculosis.

iv. Patients with positive tuberculin test with additional risk factors such as **diabetes mellitus, malignancy, silicosis, AIDS, etc.**

❖ Role of Glucocorticoids in Tuberculosis

- Tuberculosis is a relative **contraindication** for the use of **glucocorticoids.**



- Glucocorticoids may be used under the cover of effective antitubercular therapy for tuberculosis of serous membranes **(pleura, pericardium, meninges, etc.), tuberculosis of the eye, larynx, genitourinary tract** and to **treat hypersensitivity reactions** to antitubercular drugs.

ANTI- LEPROTICS DRUGS

Points to be covered in this topic

1. INTRODUCTION OF LEPROTICS
2. CLASSIFICATION OF ANTI LEPROTICS AGENTS
3. MOA,PHARMACOKINETICS ,ADR,USES OF DIFFERENT CLASS OF DRUGS
4. TREATMENT OF LEPROSY

❑ INTRODUCTION

- Leprosy, caused by **Mycobacterium leprae.**
- **Chronic granulomatous** infection caused by obligate **intracellular acid fast bacilli Mycobacterium leprae.**
- **Skin, mucus membrane** and **peripheral nervous System.**

➢ **Pathogenicity** : survive with in **macrophages** and **schwann cells**

- Prevalent in lower socio economic strata .
- Discovered by **Gerhard Armauer Hansen in 1873.**
- It is Also known as **Hansen's disease**

❖ Types of leprosy (2 types)

i. **Paucibacillary leprosy (PBL)**

ii. **Multibacillary leprosy (MBL)**

i. **Pauci-bacillary leprosy**: It is the form of leprosy in which **five or less skin lesions are present** and includes TT, BT and indeterminate leprosy.

ii. **Multi-bacillary leprosy**: It includes **leprosy with more than five skin lesions or smear positive cases** even if the lesions are less than five. BB, BL and LL leprosy are multi bacillary.

- **Borderline (BB), borderline lepromatous (BL)** and **lepromatous leprosy (LL)**, hence, these groups are called **as multibacillary leprosy (MBL)**
- **Borderline tuberculoid (BT), tuberculoid (TT)** and indeterminate (I) leprosy are referred to as **paucibacillary leprosy.(PBL)**

❖ Signs of Leprosy

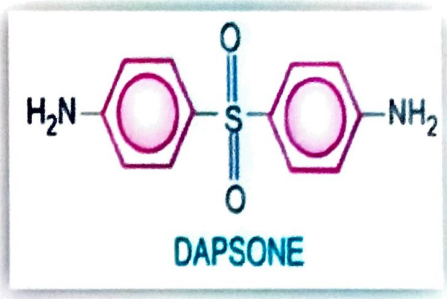
- **Skin patch or patches with a definite loss of sensation**
- **Pale or reddish or copper-coloured skin**
- **Do not itch, lack sensation to heat, touch or pain**

❑ CLASSIFICATION OF ANTILEPROSY DRUGS

CLASS	DRUGS
Sulfone	Dapsone
Phenazine dvt	Clofazimine
Antitubercular drugs	Rifampin Ethioniamide
other antibiotics	Ofloxacin Moxifloxacin , Minocyclin , clarithromycin

1. Sulfone

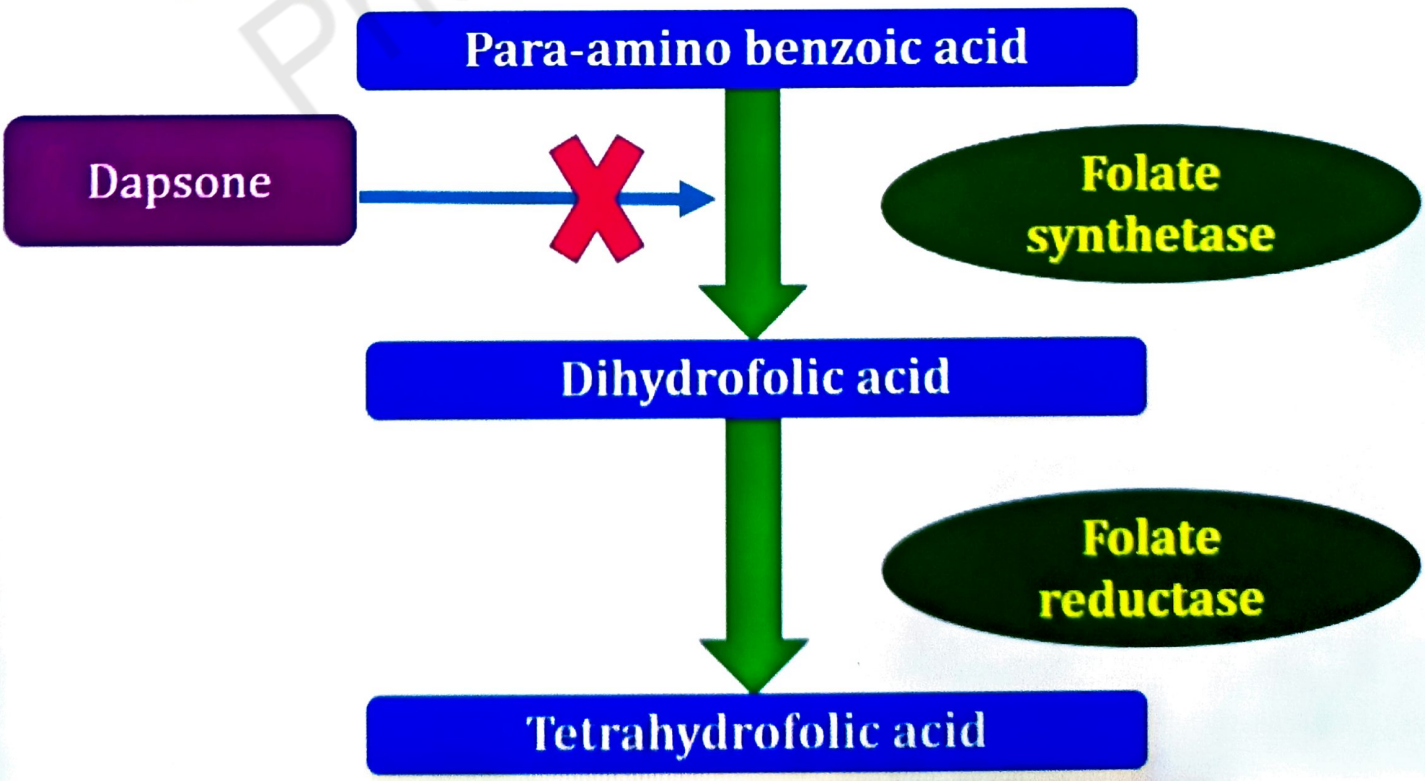
i. Dapsone



- **Dapsone is diaminodiphenylsulfone (DDS).**
- It is oldest, cheapest and most effective
- Resistance may develop if used as **monotherapy**
- Resistance- **primary and secondary (mutation of folate synthase- lower affinity)**

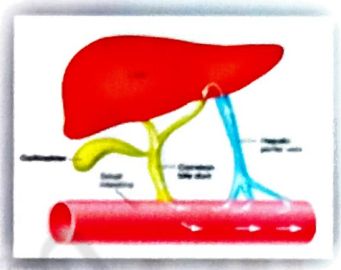
❖ Mechanism of action

- Lepra bacilli utilize ***para*-amino benzoic acid (PABA)** for the synthesis of folic acid, which, in turn, is necessary for its growth and multiplication.
- Dapsone is structurally similar to **PABA.**
- Dapsone **inhibits the incorporation of para-amino benzoic acid (PABA) into folic acid.**
- It competitively **inhibits folate synthetase enzyme** and **prevents the formation of tetrahydrofolic acid (THFA)**
- Dapsone produces **leprostatic effect.**



❖ Pharmacokinetics

- Dapsone is given **orally** & completely **absorbed from the gut.**
- It is **bound to plasma proteins**,
- It is widely distributed in the body and concentrated mainly in the **infected skin, muscle, liver, kidney**, etc.
- It is **secreted in bile** and undergoes **enterohepatic cycling.**
- Dapsone is **metabolized by acetylation .**
- It is metabolites are **excreted in urine**



❖ Adverse effect

- Haemolytic anaemia particularly in patients with **G6PD deficiency.**

❖ Side effects

- **Anorexia,**
- **Nausea, vomiting, fever, headache, allergic**
- **Dermatitis, itching**
- **Peripheral neuropathy**
- Dapsone may cause exacerbation of lesions— **'sulfone syndrome'**, which is characterized by **fever, dermatitis, pruritus, lymphadenopathy, methaemoglobinaemia , anaemia and hepatitis**

❖ SULFONE SYNDROME

Starts after **4-6 weeks of therapy**, more common with MDT Symptoms:

Fever, malaise, lymphnode enlargement, desquamation of skin, jaudice and anemia Malnourished patients

❖ Management

- Stopping of dapsone in severe cases, **corticosteroids therapy**
- Corticosteroids (prednisolone 40-60mg/day) severe cases- till reaction controlled-tapered over 8-12weeks

❖ **Dapsone contraindications** : Severe **anaemia and G-6-PD deficiency and hypersensitivity**

❖ **Uses of Dapsone**

i. **Leprosy**

ii. Also has **antiprotozoal at action (Falciparum and T.Gondii)**

iii. **Pneumocystis Jiroveci Pneumonia**

iv. **Toxoplasmosis> Dermatological Disorders - Acne, Dermatitis herpatiformis , Bullous SLE, Pemphigus**


Infection of lungs by Pneumocystis carinii

2. Phenazine derivative

i. Clofazimine

- It is a **dye with leprostatic and anti-inflammatory** properties.
- Interference with template function of DNA in **M.leprae**
- Alteration of membrane stucture and its transport function.
- Disruption of **mitochondrial electron transport chain.**

❖ **Mechanism of action**

- **Clofazimine binds to mycobacterial DNA to inhibit its template function.**
- It also has **activity against dapsone-resistant organism**

❖ **Pharmacokinetics**

- It is given **orally—fatty meal increases its absorption.**
- It accumulates in tissues— **$t_{1/2}$ is 70 days.**

❖ **Adverse effect**

- **Reddish– black Discolouration of the hair, tears, sweat, urine**
- **Pigmentation of the conjunctiva and cornea**
- **Nausea, vomiting, diarrhoea, and abdominal pain**
- **Phototoxicity**

❖ Uses of Clofazimine

- It is used to **multidrug therapy of leprosy.**

3. Antitubercular drugs

Rifampin , Ethioniamide

i . Rifampin

- **Tuberculocidal drug** is also the most potent cidal drug for **M.Leprae .**

❖ Mechanism of action

Inhibits bacterial DNA dependent RNA synthesis by inhibiting **bacterial DNA dependent RNA polymerase**

❖ Pharmacokinetics

- Rapidly renders **leprosy patient non contagious**
- **99.99% bacilli killed with in 3-7 days**, Lesions start regressing in **2 months**

❖ **Used** in **multidrug therapy** Shortens duration of treatment.

- Used in **combination with dapsone**, it shortens the duration of treatment. Given alone—resistance develops.
- Rifampicin is now an important drug in **multidrug regimens for leprosy**
- **Dose :- 600mg monthly dose given**

ii. Ethioniamide

- Ethionamide is **bactericidal** to **lepra bacilli** but is **more expensive and more toxic than dapsone.**
- It can cause **gastric irritation, peripheral neuritis and hepatotoxicity.**
- Ethionamide can be used in **multidrug regimen** in patients who cannot tolerate clofazimine.

4. Other antibiotics

Ofloxacin, Moxifloxacin , Minocyclin , clarithromycin

Fluoroquinolones:

- Many fluoroquinolones (FQs) like **Ofloxacin, pefloxacin, moxifloxacin, Sparfloxacin** are highly **active against *M.leprae***, but **ciprofloxacin has poor activity.**

i. Ofloxacin is **lepricidal** and is suitable for use in **multi-drug regimens** in leprosy along with rifampicin.

- **Ofloxacin 400 mg + rifampicin 600 mg** daily for **28 days** has been used in short-term clinical trials.

ii. Moxifloxacin is the **most potent FQ against *M. leprae***. Recently, it has been tried in some combination regimens with good clinical and bacteriological results.

iii. Minocycline

- It is a tetracycline, has been found to have useful **activity against *M. leprae*** and is being tried in combination regimens to shorten the duration of treatment.
- It is given in the dose of 100 mg daily but **should not be used in children and pregnant women.**

iv. Clarithromycin

- **It is** a macrolide antibiotic, has bactericidal **activity against *M. leprae.***
- Given **500 mg daily for 28 days** can kill 99% of viable bacilli.

❑ TREATMENT OF LEPROSY

- Leprosy is a chronic granulomatous infection **caused by *Mycobacterium leprae*.**
- Primarily affecting skin, **mucous membranes and nerves.**

✓ Types of leprosy

- **Lepromatous (LL)**
- **Borderline lepromatous (BL)**
- **Borderline (BB)**
- **Borderline tuberculoid (BT)**
- **Tuberculoid(TT)**

Tuberculoid leprosy	Lepromatous leprosy
Anaesthetic patch	Diffuse skin and mucous membrane infiltration, nodules
Cell mediated immunity (CMI) is normal	CMI is absent
Lepromin test—positive	Lepromin test—negative
Bacilli rarely found in biopsies	Skin and mucous membrane lesions teeming with bacilli
Prolonged remissions with periodic exacerbations	Progresses to anaesthesia of distal parts, atrophy, ulceration, absorption of digits, etc.

❖ Chemotherapy of Leprosy

- leprosy has been classified into two **types—multibacillary and paucibacillary leprosy**

➢ **The objectives and need for MDT are**

i. To make the patient noncontagious as early as possible by **killing the dividing bacilli.**

ii. To prevent the development of **drug-resistant bacilli.**

iii. To prevent **relapse**

iv. To **shorten the duration of effective therapy**

➢ **Treatment Schedules of Leprosy**

✓ All drugs are **administered orally.**

1. **For multibacillary leprosy (LL, BL and BB)**

- **Rifampin 600 mg once monthly +**
- **Clofazimine 300 mg once monthly** } **(supervised)**

+

- **Dapsone 100 mg daily +**
- **Clofazimine 50 mg daily** } **(Unsupervised self administered)**
- The duration of treatment is **1 year**, and later the patient should be followed up for a period of **3–5 years.**

  If clofazimine is unacceptable, the alternative drug used is **ethionamide 250 mg daily, unsupervised.**

2. **For paucibacillary leprosy (TT, BT and I)**

- **Rifampin 600 mg once monthly (supervised) +**
- **Dapsone 100 mg daily (unsupervised).**

The duration of treatment is **6 months**, and later the patient should be followed up for a period of 1–2 years

❖ Multidrug therapy (MDT) of leprosy

- Multidrug therapy with **rifampin, dapsone and clofazimine** was introduced by the WHO in 1981.
- This was implemented under the **NLEP in 1982.**

➢ **MDT is the regimen of choice for all cases of leprosy.**

Its **advantages** are:

- It is effective in cases with **primary dapsone resistance**.
- It prevents emergence of **dapsone resistance**.
- It **reduces total duration of therapy** and chances of **relapse to < 1%**.
- The **efficacy, safety and acceptability of MDT for both PBL and MBL is excellent.**
- **No resistance to rifampin** has developed after use of **MDT, and *M. leprae*** isolated from relapse cases have remained sensitive to it.

❖ NLEP Classification of leprosy

Paucibacillary leprosy (PBL)	*Multibacillary leprosy (MBL)*
• 1-5 skin lesions	• 6 or more skin lesions
• No nerve or only one nerve involvement, ± 1–5 skin lesions.	• > 1 nerve involved irrespective of number of skin lesions
• Skin smear negative at all sites	• Skin smear positive at any one site

❖ MDT Therapy of leprosy

	Multibacillary	***Paucibacillary***
Rifampin	600 mg once a month supervised	600 mg once a month supervised
Dapsone	100 mg daily self administered	100 mg daily self administered
Clofazimine	300 mg once a month supervised + 50 mg daily self administered	—
Duration	12 months	6 months

Child dose		
Rifampin	:	10 mg/kg once monthly
Clofazimine	:	1 mg/kg daily + 6 mg/kg once monthly
Dapsone	:	2 mg/kg daily

- **Relapse of leprosy the same MDT (12 months for MBL** and **6 months for PBL)** is Started on confirmation of relapse.
- **Leprosy and TB coinfection** MDT for leprosy is continued, but rifampin is given Daily as for treatment of TB.
- **Leprosy in HIV patients** no association of leprosy with HIV infection has been found.

MDT for leprosy can be given safely to **HIV +ive patients** and to those receiving anti-retroviral therapy .

❖ Reactions in leprosy

1. Type-1 lepra reaction (reversal reaction)

- It is a delayed type of **hypersensitivity** and is seen in tuberculoid leprosy.
- There are signs of inflammation in the existing skin lesions—they **become red, warm and swollen.**
- New lesions may appear.
- Nerves are frequently affected; when they occur after the initiation of therapy, they are known as **reversal reactions.**
- It is treated with **clofazimine or prednisolone.**

2. Type-2 lepra reaction [erythema nodosum leprosum(ENL)]

- It occurs in **lepromatous leprosy**.
- It is a **type-III hypersensitivity reaction** (Arthus-type).
- There is erythema **nodosum—red, painful, tender cutaneous and subcutaneous nodules.**
- **Nerves** may be affected.
- The **type-2 reaction** may be due to release of antigen from the dying **lepra bacilli.**
- Severe form of **type-2 reaction** is treated with **thalidomide**, but it should **not be prescribed during pregnancy**.
- The other drugs used are **aspirin, clofazimine, chloroquine and prednisolone.**

ANTIFUNGAL DRUGS

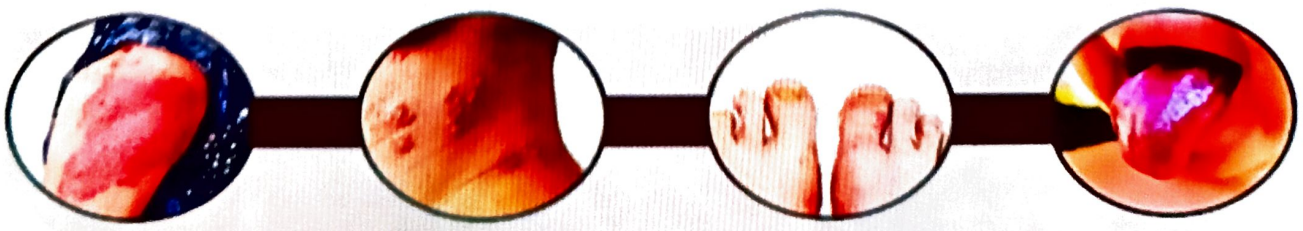
Points to be covered in this topic

1. INTRODUCTION
2. CLASSIFICATION OF ANTI FUNGAL AGENTS
3. MOA,PHARMACOKINETICS ,ADR,USES OF DIFFERENT CLASS OF DRUGS

❑ INTRODUCTION

- A fungal infection, also called **mycosis**, is a **skin disease caused by a fungus.**
- There are **millions of species of fungi**.
- They live in the **dirt,** on **plants**, on **household surfaces**, and on your skin.
- Sometimes, they can lead to skin problems like **rashes or bumps.**
- These are drugs used for superficial and deep (systemic) fungal infections
  - ✓ **Superficial fungal** infections include infections of the **skin, mucous membrane, hair and nails**
  - ✓ **Systemic fungal** infections may be **life-threatening**, particularly In immune compromised patients.

❖ Sign & symptoms of fungal infection



SKIN RASH | SKIN LESIONS | NAIL BED INFECTION | ORAL THRUSH

❑ CLASSIFICATION OF ANTIFUNGAL DRUGS

CLASS	SUB CLASS		DRUGS
Antibiotics	Polyenes		Amphotericin B, Nystatin
	Hetero cyclic benzofuran		Griseofulvin
	Echinocandis		Caspofungin micafungin anidulafungin
Antimetabolites			Flucytosine
Azoles	Imidazoles	Topical	Clotrimazole , Econazole , miconazole , oxiconazole
		Systemic	Ketoconazole
	Triazoles		Fluconazole Itraconazole voriconazole Posaconazole
Allylamine			Terbinafine
Other topical agents			Tolnafate ,undecylenic acid , benzoic acid , ciclopirox olamine , butenafine

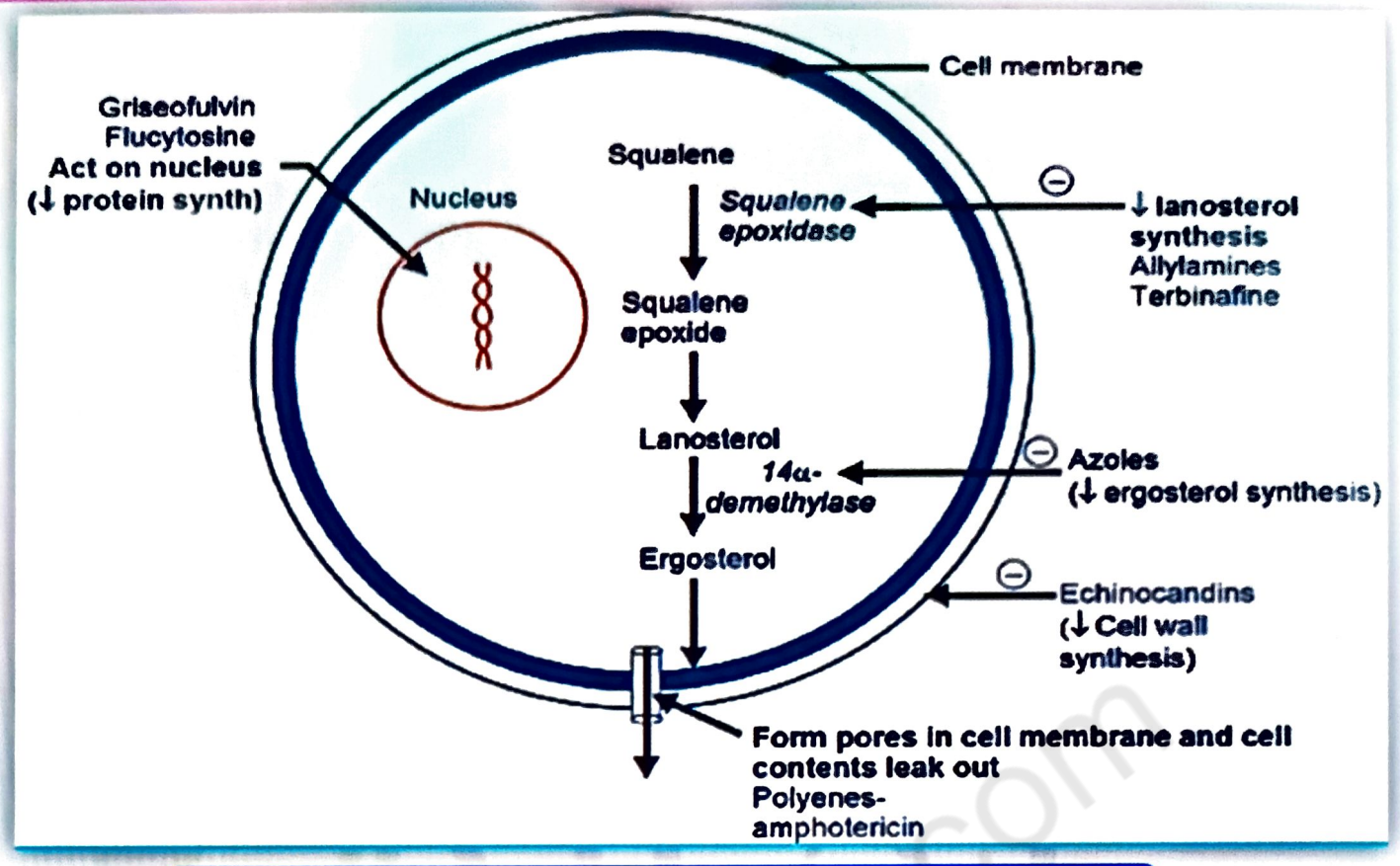


Fig:- Site of action of antifungal drugs

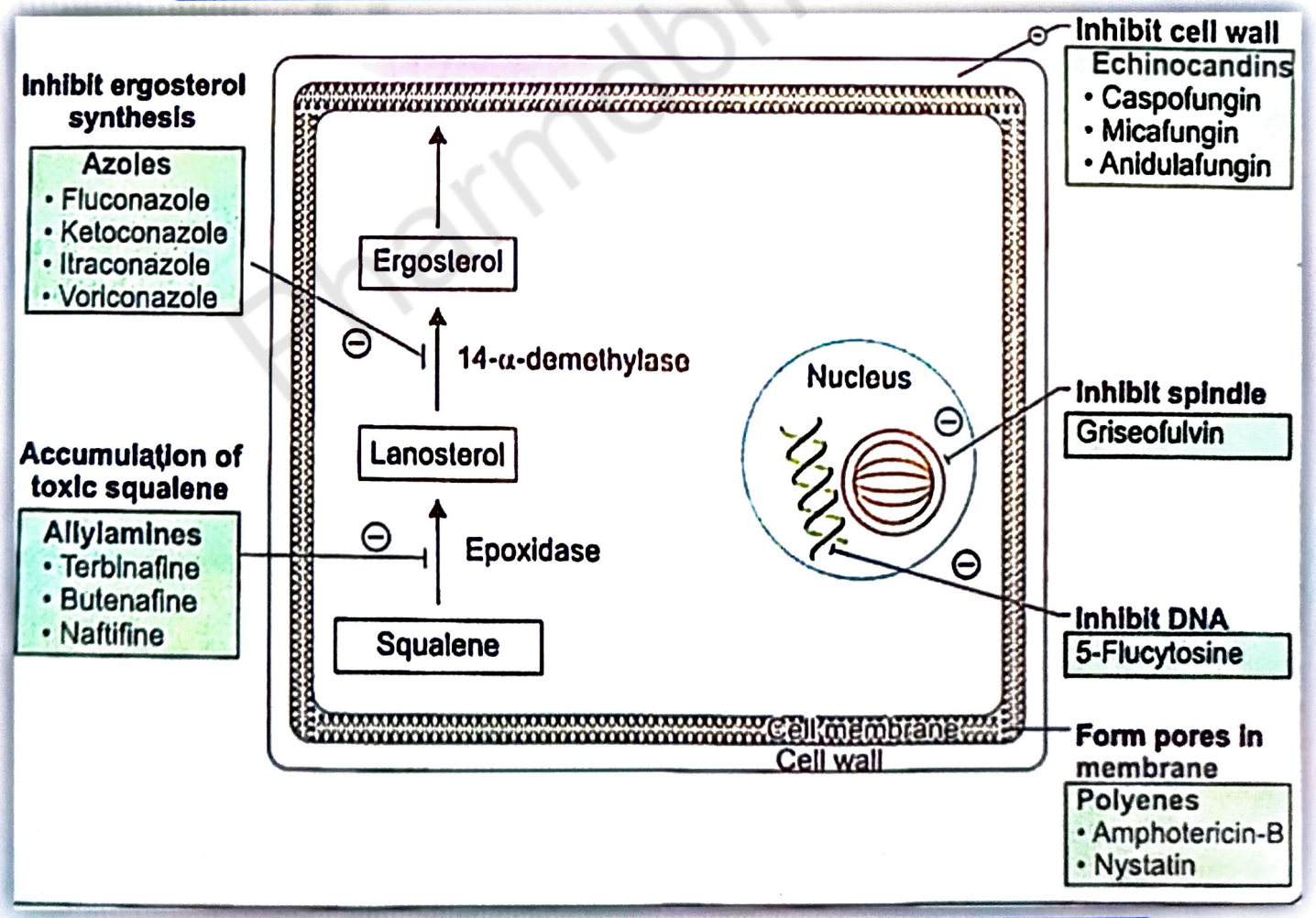


Fig:- Mechanism of action of antifungal drugs

I. Antibiotics

Polyenes :- Amphotericin B, Nystatin

1. Polyenes

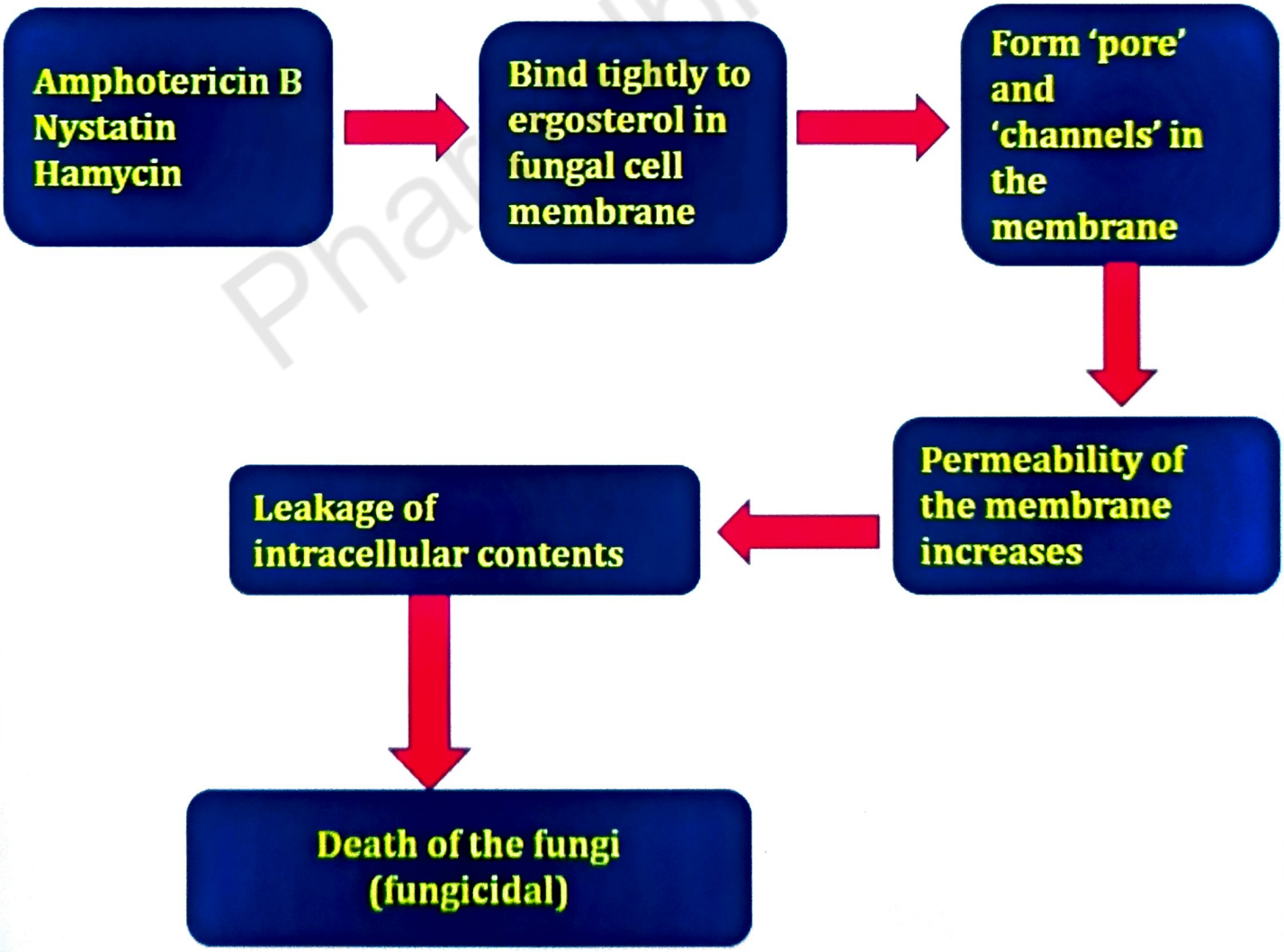
The name **polyene** is derived from their highly **double-bonded structure.**

i. Amphotericin B

- It is obtained from ***Streptomyces nodosus.***
- Amphotericin B (AMB) is a **broad-spectrum** antifungal antibiotic.

❖ Mechanism of action

- Fungal cell membrane contains a sterol, which resembles cholesterol and is called '**ergosterol**'.
- **Bind to fungal cell membrane ergosterol**



❖ Antifungal spectrum

- AMB is effective against **Cryptococcus, Coccidioides, Candida, Aspergillus, Blastomyces, Histoplasma, Sporothrix, fungi causing mucormycosis,** etc.
- It is **fungicidal at high and static at low concentrations**

❖ Resistance

- AMB during therapy has been rarely noted among ***Candida*** in a selected group of **leucopenic cancer patients**, but it is not problem in the clinical use of the drug.
- **AMB** is also active on various species of ***Leishmania,*** a protozoa.

❖ Pharmacokinetics

- Amphotericin B is **not absorbed from the gut** hence is not suitable **orally for systemic infections**.
- It is highly **bound to plasma proteins** and sterols in tissues, widely distributed to various tissues but **does not cross the BBB.**
- It is **metabolized in liver** and **excreted slowly in urine and bile**.

❖ Adverse effects

- Acute reactions are **fever, chills, headache, dyspnea**
- CNS Toxicity :- Phlebitis at the site of injection, **nausea and vomiting,**
- **Anaemia** and **electrolyte disturbances**

  anaemia is less with lipid formulations.
- **Nephrotoxicity with Azotaemia**
- **Hepatotoxicity**
- **Headache and convulsions**

  may occur on **intrathecal administration.**

❖ Interactions

- **Flucytosine (5-FC) has supraadditive action with AMB** in the case of fungi sensitive to both (AMB increases the penetration of 5-FC into the fungus).
- **Aminoglycosides, vancomycin, cyclosporine** and other nephrotoxic drugs enhance the renal impairment caused by AMB.

❖ Formulations of amphotericin B

- **Amphotericin B is poorly water soluble**; hence, **intravenous preparation** is made with **deoxycholate—conventional** amphotericin B (C-AMB).
- **ABCD (AMB colloidal dispersion), ABLC (AMB–lipid complex) and liposomal AMB (L-AMB)** are the lipid-based new formulations of AMB.
- They are **less nephrotoxic than C-AMB.**

❖ Uses

- AMB in the treatment of many fungal diseases.
- AMB is useful for various systemic fungal infections like **aspergillosis, cryptococcosis, sporotrichosis, candidiasis, cryptococcal meningitis**, etc.
- Amphotericin B can be applied topically for **oral, vaginal and cutaneous candidiasis, fungal corneal ulcer and otomycosis**

❖ **Mnemonic (Salient features of amphotericin)**

✓ **I Love AMPHOTERICIN**

L—Lipid formulation

A—Anemia

M—Muscle spasms

P—Paracetamol before amphotericin B

H—Hepatotoxicity, headache, hypotension

O—Orally given in gut infection

T—Topical use: rashes

E— Decrease Erythropoietin

R—Renal impairment

I—Irreversible nephropathy (long-term use)

C—Chills

I—IV (used)

N—Neurotoxicity

ii. Nystatin

- It is Obtained from *S. noursei* .
- it is similar to AMB in , **MOA antifungal action and other properties.**
- It is is poorly absorbed from the **skin** and **mucous membranes.**
- It is highly toxic for systemic use.
- It is used only topically in ***Candida*** **infections.**
- It is available as **suspension, ointment, cream, powder and tablet.**

❖ Uses

i. **In dentistry**: Nystatin is used topically for oral **candidiasis, angular cheilitis and antibiotic-associated stomatitis.**

ii. Nystatin can be used for **monilial vaginitis** —1 lac U tab is to be inserted twice daily.

iii. Other uses include **oropharyngeal, corneal, conjunctival and cutaneous candidiasis.**

iv. It is used only locally for **superficial candidiasis.**

❖ Adverse effects

- **Nausea** and **bitter taste.**

Dose :- **Nystatin oral suspension 5 mL (1 lakh units/mL) to be swished and swallowed 4–5 times a day for 14 days.**

iii. Hamycin

- It is similar to **Nystatin .**
- It is used topically for **cutaneous candidiasis and otomycosis.**

2. Hetero cyclic benzofuran

Hetero cyclic benzofuran :- Griseofulvin

i. Griseofulvin

- Griseofulvin is a **fungistatic** derived from ***Penicillium griseofulvum.***
- Dermatophytosis **(caused by *trichophyton, microsporum and epidermophyton).***
- Griseofulvin is the antifungal given orally for **superficial Dermatophytosis.**
- It is **not effective topically.**

❖ Mechanism of action

- Disruption of **miotic spindle** and **inhibition of fungal mitosis**
- Griseofulvin is Interacts with polymerized microtubules
- Disrupts the mitotic spindles Spindle poison – inhibits fungal mitosis (fungistatic)

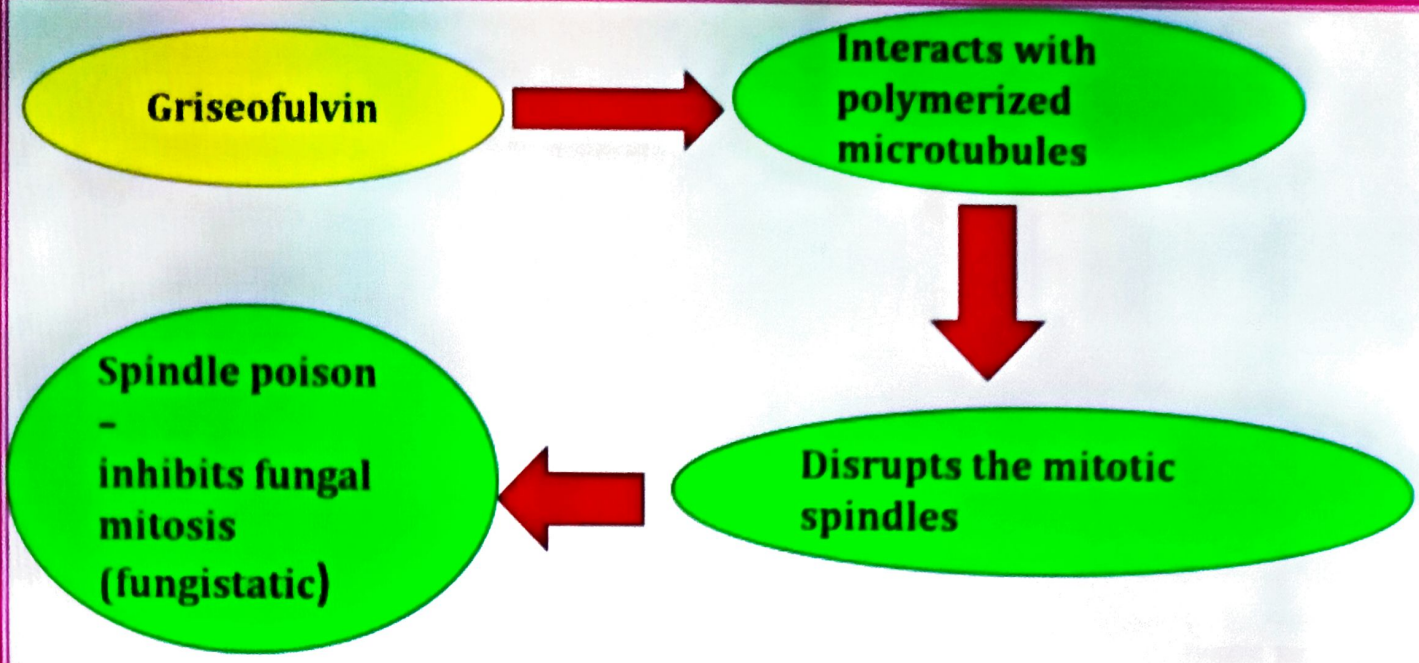


Fig:- Mechanism of action of Griseofulvin

❖ Pharmacokinetics

- Griseofulvin is administered **orally.**
- Its **bioavailability is increased** by taking with fatty food and by using ultrafine preparation.
- It gets concentrated in **keratinized tissues** such as **skin, hair, nails**, etc.
  It is an **enzyme inducer**; thus, it reduces the effectiveness of **warfarin and oral contraceptives.**
- It has **Disulfiram like action**, hence can cause **intolerance to alcohol.**
- It is **metabolized in liver** and **excreted in urine.**

❖ Adverse effects

- **Headache**
- **Rashes**
- **Peripheral neuritis**
- **Vertigo**
- **Blurred vision**
- **GI effects** such as **nausea, vomiting, diarrhoea, heartburn**

❖ Uses

- Griseofulvin is used in the treatment of **dermatophytic infections** like **tinea (ringworm) infections (*Tinea capitis, Tinea barbae, Tinea corporis, Tinea pedis*).**

3. Echinocandis

Echinocandis :- Caspofungin , micafungin , anidulafungin

It is potent semisynthetic antifungal antibiotics with a complex cyclic lipopeptide structure, which stand out due to their low toxicity compared to AMB.

i. Caspofungin

It is active mainly against ***Candida*** **and** ***Aspergillus.***

❖ Mechanism of action

- Fungal cell wall synthesis inhibition

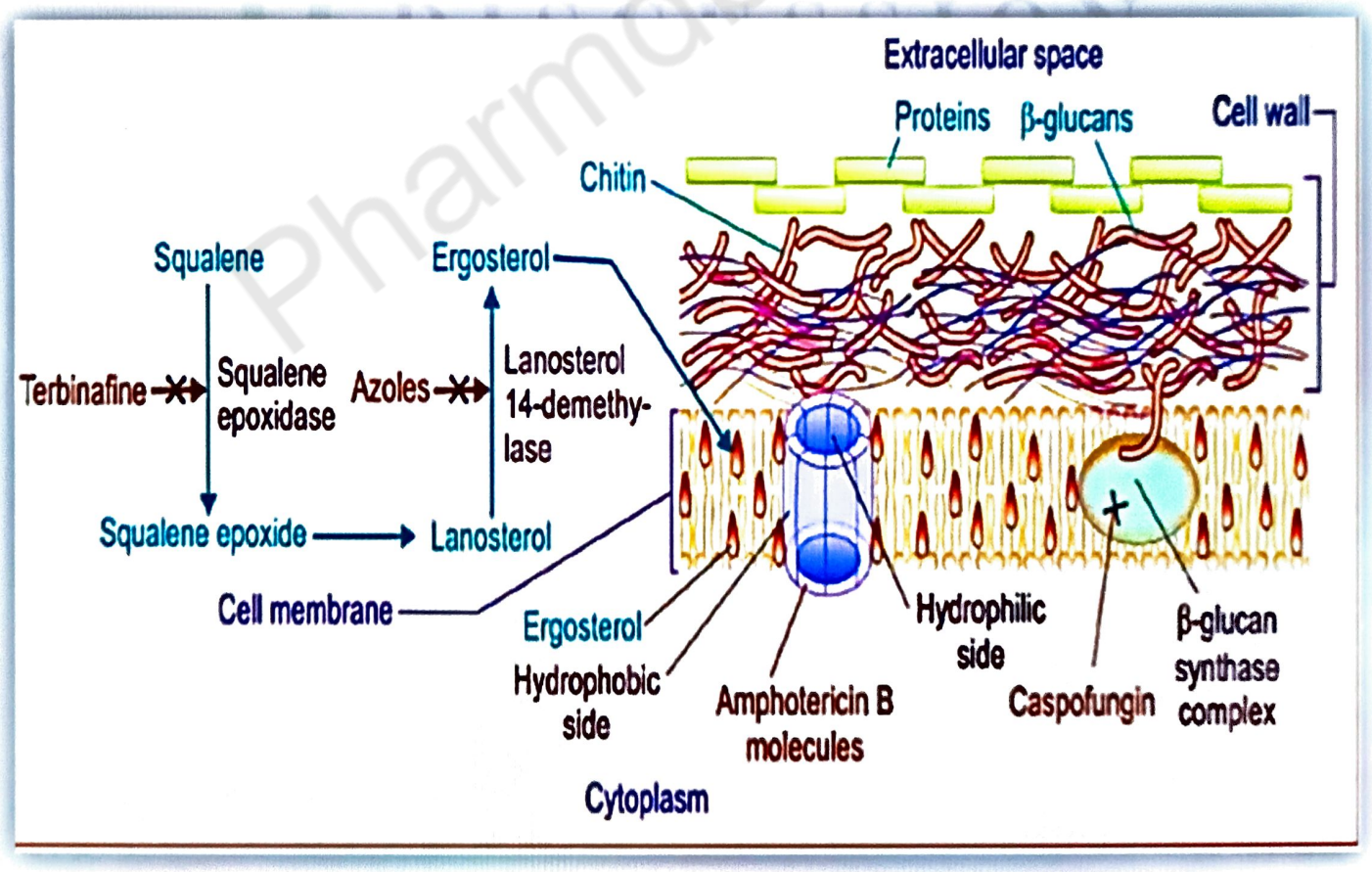
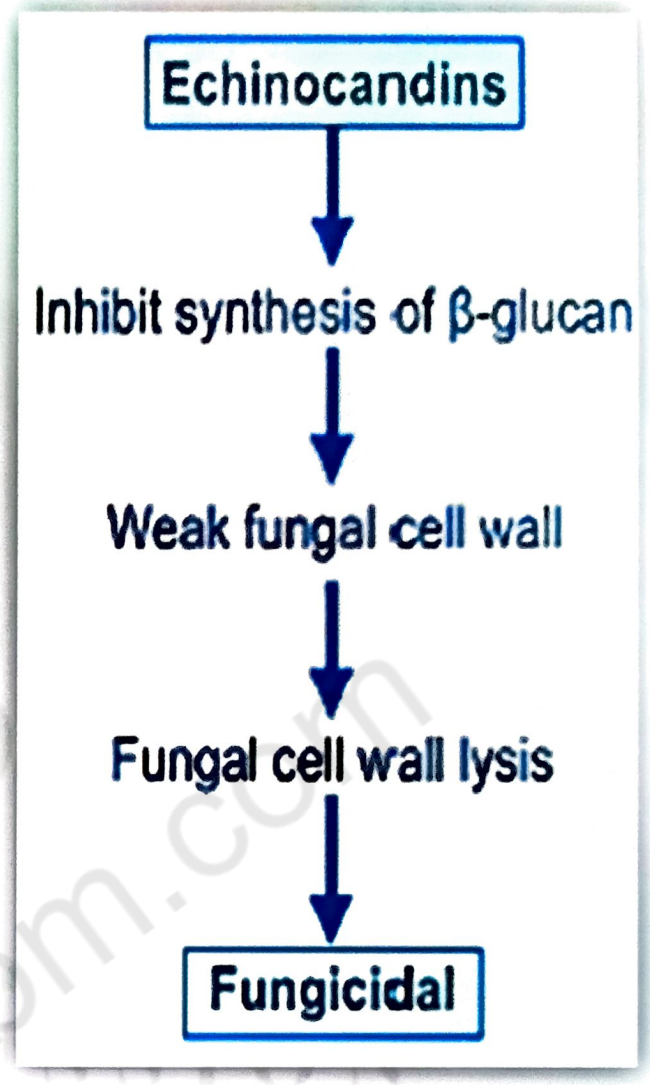


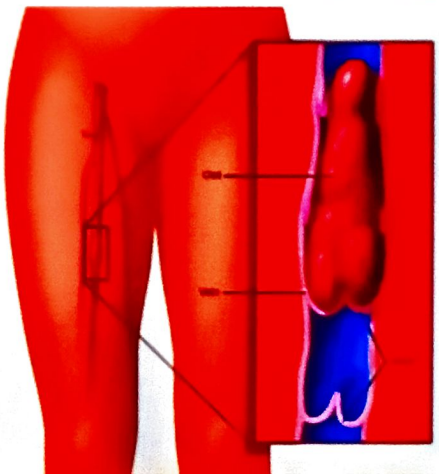
Fig :- Mechanism of action of Caspofungin

- **Inhibits the synthesis of β-1, 3-glucan**, which is a unique component of the fungal cell wall.
- **β-glucans are synthesized in the fungal plasma membrane** by a complex of β-glucan synthase enzymes which is **inhibited by caspofungin**.
- **Cross linking between chitin (a fibrillar polysaccharide) and β-1, 3-glucan** gives toughness to the fungal cell Wall.
- Weakening of the cell wall by **caspofungin** leads to osmotic susceptibility of fungal cell, which then succumbs.



❖ Pharmacokinetics

- Caspofungin is **not absorbed orally**; has to be infused **I.V.** as freshly prepared aqueous solution.
- It is distributed into tissues, **but does not enter CSF**.
- Metabolism is extensive and metabolites are **excreted in urine** as well as **faeces with a plasma t½ of 10 hours.**



❖ Adverse effects

Thrombophlebitis.

❖ Uses

i. **Candida infections**

ii. **Invasive aspergillosis**

ii. Micafungin

- It is **MOA , pharmacokinetics uses similar to caspofungin.**
- Its t½ is some what longer (12–15 hours).
- In addition to **esophageal candidiasis and candidaemia, micafungin (50 mg I.V./day)**
- It is is indicated for prophylaxis of *candida* infections in bone marrow transplant patients, but not for aspergillosis.

iii. Anidulafungin

- It is the third echinocandin with still longer **t½ (~36 hours).**
- **MOA , pharmacokinetics uses similar to caspofungin.**

II. Antimetabolites Flucytosine

i. Flucytosine (5-FC)

- fluorinated pyrimidine **effective against *Cryptococcus neoformans*** and some strains of ***Candida.***
- Flucytosine is a **prodrug.**
- Flucytosine has **synergistic activity** with amphotericin B and azole antifungals.

❖ Mechanism of action

Inhibition of nucleic acid synthesis

- It is **converted into 5-fluorouracil** and then **to 5-fluorodeoxyuridylic acid which is an inhibitor of thymidylate synthesis.**
- **Thymidylic acid** is a component of DNA.
- The fungal selectivity of **5-fc depends** on the fact that mammalian cells (except some marrow cells) have low capacity to convert 5-fc into 5 fluorouracil.

❖ Pharmacokinetics

- Flucytosine is **well absorbed**, reaches all body fluids including **CSF** .
- **Excreted by the kidneys**.

❖ Adverse effects

- **Bone marrow depression**
- **Gastrointestinal disturbances**

❖ Uses

Flucytosine is used with **amphotericin B in cryptococcal meningitis and systemic candidiasis** because:

i. Used alone, resistance develops rapidly

ii. It is **synergistic with other drugs**

iii. Flucytosine is also used with itraconazole in **chromoblastomycosis**

III. Azoles

1. Imidazoles

a) Topical :- Clotrimazole , Econazole , miconazole , oxiconazole

b) Systemic :- Ketoconazole

a) Topical :- Clotrimazole , Econazole , miconazole , oxiconazole

- The azoles have **broad-spectrum antifungal activity** covering **dermatophytes, Candida,**
- other fungi involved in **deep mycosis (except mucor), Nocardia and Leishmania.**

❖ Mechanism of action

- **Inhibition of ergosterol systhesis.**
- **Azoles inhibit the synthesis of ergosterol**, an important component of the fungal cell membrane

- Azoles inhibit the **fungal cytochrome P450 enzyme lanosine 14α-demethylase** which catalyses the **convertion of lanosterol to ergosterol.**
- Thus it results in **ergosterol deficiency** which results in **weak fungal cell membrane** and **fungal replication.**
- They also interfere with the function of some **fungal enzymes and inhibit the growth of the fungi.**

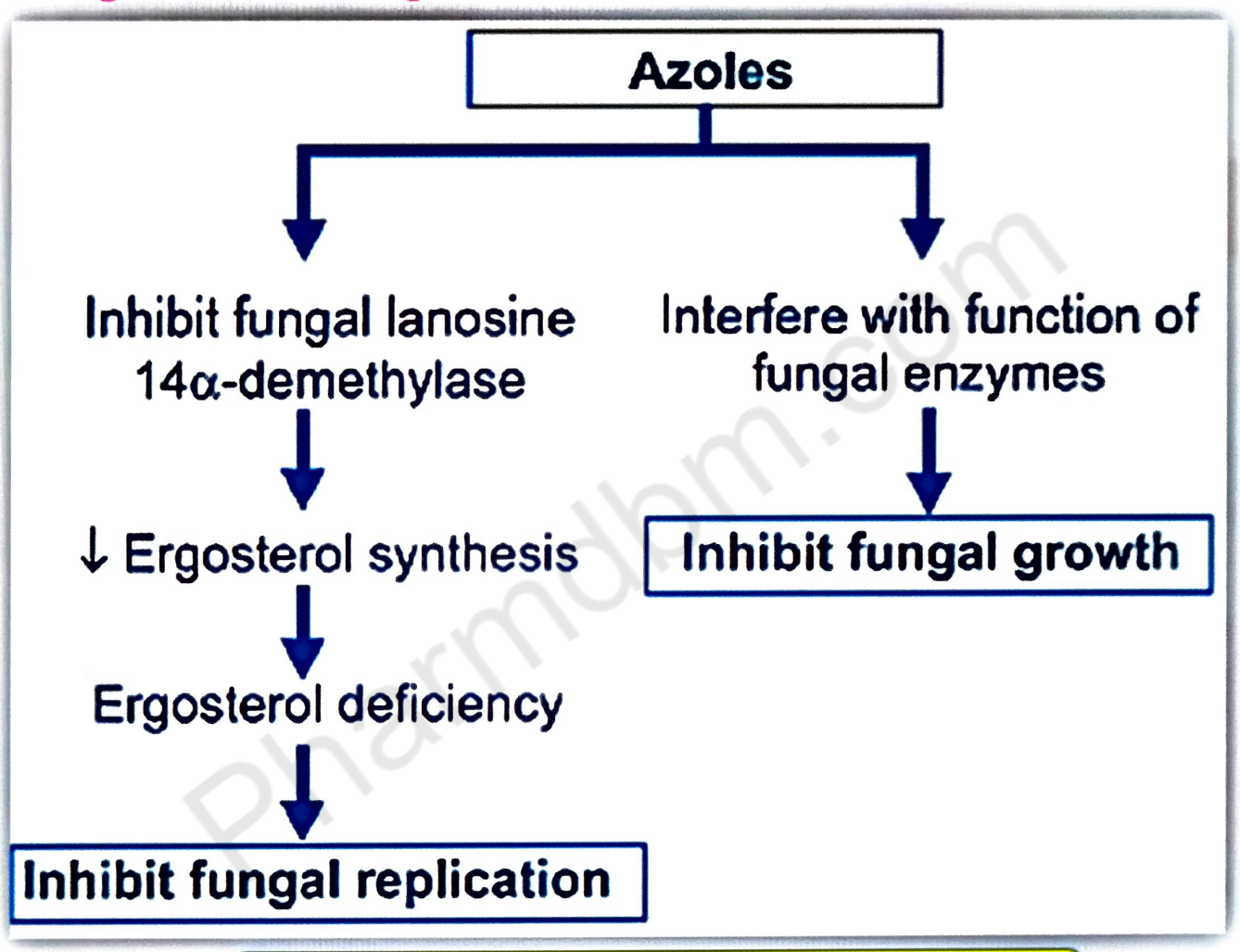


Fig :- Mechanism of action of azole

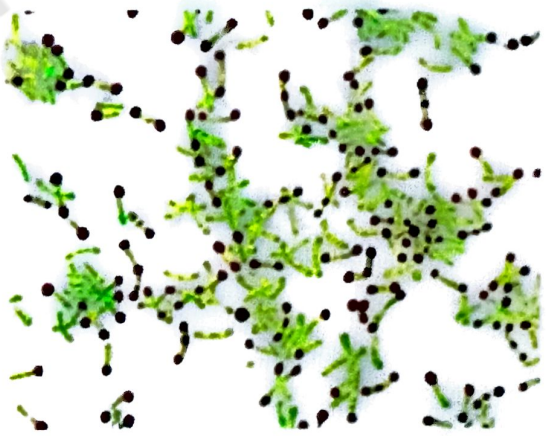
- Azoles have **higher affinity to fungal** than human **CYP 450 enzymes**, some selective activity is attained.
- Many of **fluconazole-resistant *Candida*** respond to **itraconazole or to voriconazole.**
- Mutation of the **gene encoding for fungal 14- α demethylase enzyme** underlies azole resistance.

❖ Antifungal spectrum

- It have a **broad-spectrum antifungal activity**.
- They **inhibit dermatophytes, Blastomyces dermatitidis, Candida, Cryptococcus neoformans, H. capsulatum, coccidioides, some paracoccidioides and other deep mycoses.**

i. Clotrimazole

- It is the most commonly used topical imidazole effective in the treatment of **tinea infections like ringworm.**
- **Athletes' foot, otomycosis and oral/cutaneous/ vaginal candidiasis** have responded in >**80% cases.**
- It is also effective in skin infections caused by **Corynebacteria**, but like most topical antifungals, has poor efficacy in **tinea capitis (scalp) and tinea unguium (nails).**



❖ Side effect

- **Local irritation with stinging**
- **Burning sensation occurs**

ii. Econazole

- It is similar to clotrimazole.
- **Penetrates superficial layers of the skin** and is **highly effective in dermatophytosis, otomycosis,oral thrush,** but is somewhat inferior to **clotrimazole in vaginitis.**

iii. Miconazole

- It is a **highly efficacious (>90% cure rate)** drug for **tinea, pityriasis versicolor , otomycosis, cutaneous and vulvovaginal candidiasis.**
- Because of its **good penetrating power, single application on skin** acts for a few days.

- **Irritation after cutaneous application** is infrequent, but a **higher incidence of vaginal irritation** is reported in comparison to **clotrimazole**

iv. Oxiconazole

- **Imidazole antifungal effective** in **tinea** and other **dermatophytic infection**, as well as in **vaginal candidiasis.**
- **Local irritation** can occur.

b) Systemic :- Ketoconazole

i. Ketoconazole

- It is the first orally effective **broad-spectrum antifungal drug,**
- It is useful in both **dermatophytosis** and **deep mycosis.**
- **KTZ inhibits the biosynthesis of adrenal and gonadal steroids** in humans—resulting in **gynaecomastia, infertility, decreased libido, azoospermia, menstrual irregularities and hypertension.**
- This steroid suppression effect of KTZ limits its use.

❖ Pharmacokinetics

- It is **well-absorbed** from the **gut.**
- **Food** and **low gastric pH** enhance absorption.

❖ Adverse effects

- Ketoconazole produces more side effects than **itraconazole** or **fluconazole**
- Side effects are **nausea** and **Vomiting.**
- **Loss of appetite, headache , paresthesia , rashes** and **hair loss.**
- It decreases **androgen production From testes, and displaces testosterone** from **protein binding sites. Gynaecomastia, loss of hair and libido,** and **oligozoospermia** may develop

- **Menstrual irregularities** occur in some women due to **suppression of estradiol synthesis.**

❖ Interaction

i. **H_2 blockers, proton pump inhibitors and antacids decrease oral absorption of KTZ by reducing gastric acidity.**

- ✓ **Rifampin, phenobarbitone, carbamazepine and phenytoin induce KTZ metabolism and reduce its efficacy.**

ii. **Ketoconazole inhibits CYP450 enzymes, especially CYP3A4, CYP2C9; CYP2C19 and raises the blood levels of several drugs including:**

- ✓ **Phenytoin Digoxin Carbamazepine Omeprazole Diazepam Cyclosporine Haloperidol Nifedipine and other DHPs Warfarin HIV protease inhibitors Sulfonylureas Statin.**

❖ Uses

i. **Dermatophytosis**

ii. Used as a **lotion or shampoo,**

iii. KTZ is quite effective in **seborrhoea of scalp and dandruff.**

iv. Used in **monilial vaginitis,**

v. KTZ has been used in **Cushing's syndrome** to **decrease corticosteroid production**

2. Triazoles

Triazoles :- Fluconazole, Itraconazole, voriconazole, Posaconazole

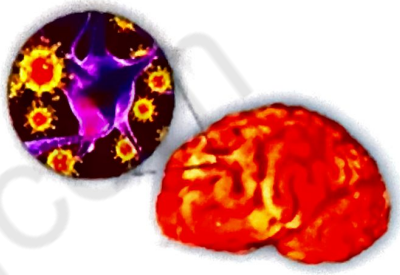
i. Fluconazole

It is a water-soluble triazole having a wider range of activity than KTZ; indications include **cryptococcal meningitis, systemic and mucosal candidiasis** .

- Both normal and **immunocompromised patients**, **coccidioidal meningitis** & some **tinea infections**

❖ Pharmacokinetics

- Flourinated triazole is **water soluble**.
- Well absorbed from the **gut**, reaches all body fluids and attains **good CSF concentration.**
- **Fungicidal** concentrations are achieved in **nails, vagina** and **saliva.**
- Fluconazole is eliminated by the **kidneys**, has a **t½ of 25 hr.**
- Fluconazole is available for **oral** and **IV use.**



❖ Adverse effects

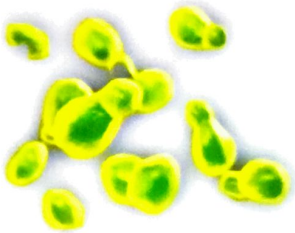
- **Mild gastrointestinal disturbances,**
- **Headache and rashes**

❖ Uses

i. **Cryptococcal meningitis**
ii. **Candidiasis**
iii. **Coccidioidal meningitis**
iv. **Leishmaniasis (off label use)**
v. **Other fungal infections**

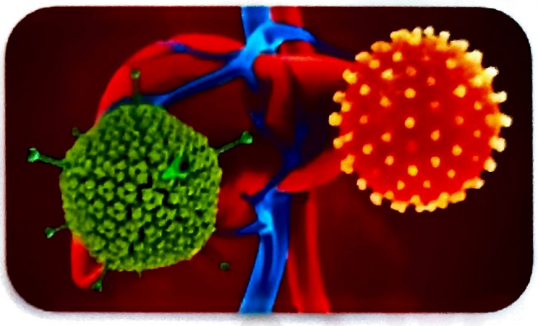
ii. Itraconazole

- This orally active triazole antifungal has a **broader spectrum of activity** than **KTZ or fluconazole**, includes few moulds like **Aspergillus** as well.
- Some fluconazole resistant ***Candida*** are susceptible.
- It is the **most potent azole.**



❖ Pharmacokinetics

- It is administered orally as well as by I.V. route.
- It is **highly bound to plasma proteins**, **does not cross BBB** and is **metabolized in liver**.
- It has a **broad spectrum of activity against many fungi** including **Aspergillus.**



❖ Adverse effects

- **Headache, dizziness**
- **GI disturbances** and **allergic reactions.**
- It can rarely cause **hepatitis** and **hypokalaemia**
- It should not be used in **pregnant women**

❖ Uses

- Itraconazole is the drug of choice in most **systemic mycoses (without meningitis) 100 mg BD with food.**
- It can be given **IV** in severe infections.
- Itraconazole can also be used in **onychomycosis, candidiasis** and **dermatophytosis, Pityriasis versicolor.**

❖ Drug interactions

- **Oral absorption** of itraconazole is **reduced by antacids, H_2 blockers and proton pump inhibitors.**
- **Rifampin, phenobarbitone, phenytoin and carbamazepine** induce itraconazole **metabolism and reduce its efficacy**

iii. voriconazole

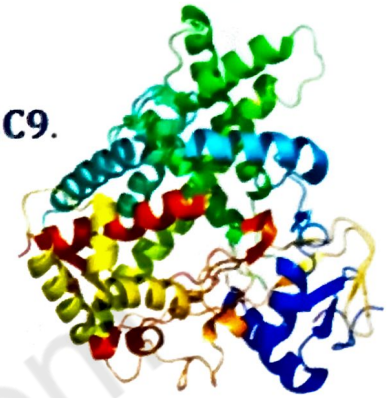
- It is a **second generation broad-spectrum triazole** introduced for difficult to treat fungal infections.
- Voriconazole is the drug of choice for **invasive *aspergillosis*,**

Disseminated infections caused by fluconazole resistant ***Candida, Fusarium*** **infections,** and **febrile neutropenia.**

- It is also active against **histoplasmosis** and **blastomycosis** .

❖ Pharmacokinetics

- It Is **completely absorbed orally**, except when taken with a fatty meal, widely distributed into tissues
- Metabolized extensively by **CYP2C19, CYP3A4, CYP2C9**.
- Excreted in **urine**.
- The **t½ is 6 hours**.



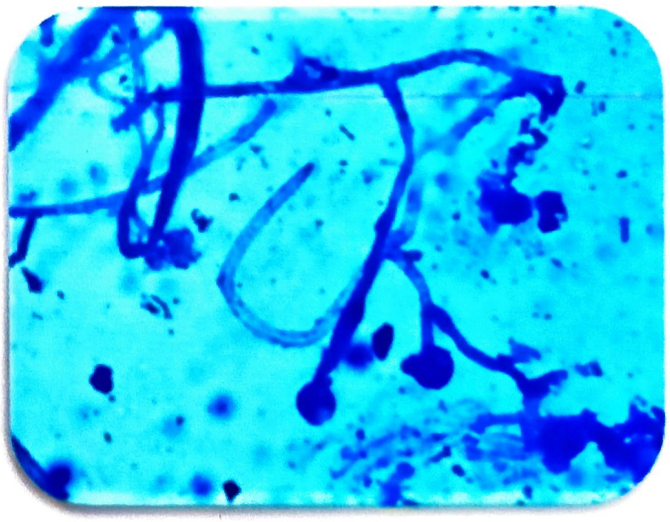
❖ Adverse effects

- **Skin rashes, visual disturbances, hepatic toxicity** and **QTc prolongation**
- IV formulation can rarely cause **anaphylaxis.**
- It is **contraindicated in pregnancy**.

❖ Uses

- Voriconazole is the drug of choice in **invasive aspergillosis** .
- Voriconazole can also be used in **oesophageal candidiasis**

iv. Posaconazole



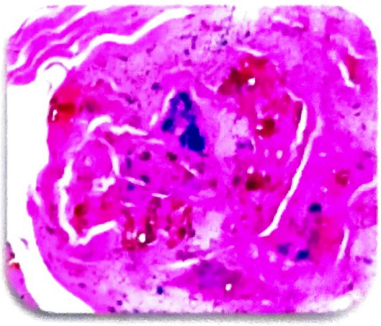
- It is a **lipophilic triazole** similar to itraconazole but with the broadest spectrum of antifungal activity among azoles including **zygomycosis** and **mucormycosis.**
- Posaconazole is indicated for **salvage therapy** of this difficult to **treat fungal infection.**

❖ Pharmacokinetics

- Administered as an **oral suspension**, **absorption of Posaconazole** is Improved by **low pH** and **fatty food**.
- It is partly metabolized by **CYP2C19** and **glucuronidation**,
- Excreted mostly unchanged in **faeces.**
- The **t½ is > 24 hours** .
- It can increase levels of drugs metabolized **by CYP3A4.**

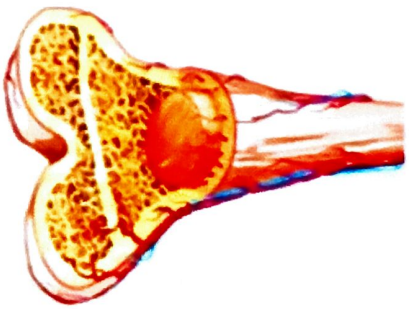
❖ Side effects

i. **Nausea**
ii. **Abdominal pain**
iii. **Loose motions**
iv. **Headache**
v. **Dizziness and drowsiness**
vi. **Anaemia**
vii. **Neutropenia**
viii. **Cardiac arrhythmias**
ix. **Visual disturbances**



❖ Uses

- Posaconazole is indicated in the treatment of refractory invasive **aspergillosis, chromoblastomycosis, fusariosis** and **coccidioidomycosis**.
- It is also indicated for the **prophylaxis of fungal infection** in patients receiving chemotherapy in **leukaemia** and in **bone marrow transplantation**.
- Drug interactions due to **inhibiton of CYP3A4** can occur



IV. Allylamine

Allylamine :- Terbinafine

i. Terbinafine

This orally and topically active drug against **dermatophytes** and **Candida**

❖ Mechanism of action

- It acts as a **noncompetitive inhibitor of 'squalene epoxidase'**, an early step enzyme which generates squalene epoxide that is converted to **lanosterol** and then to **ergosterol by fungi.**
- Terbinafine, an allylamine , **inhibits squalene 2,3-epoxidase** and **blocks ergosterol synthesis**

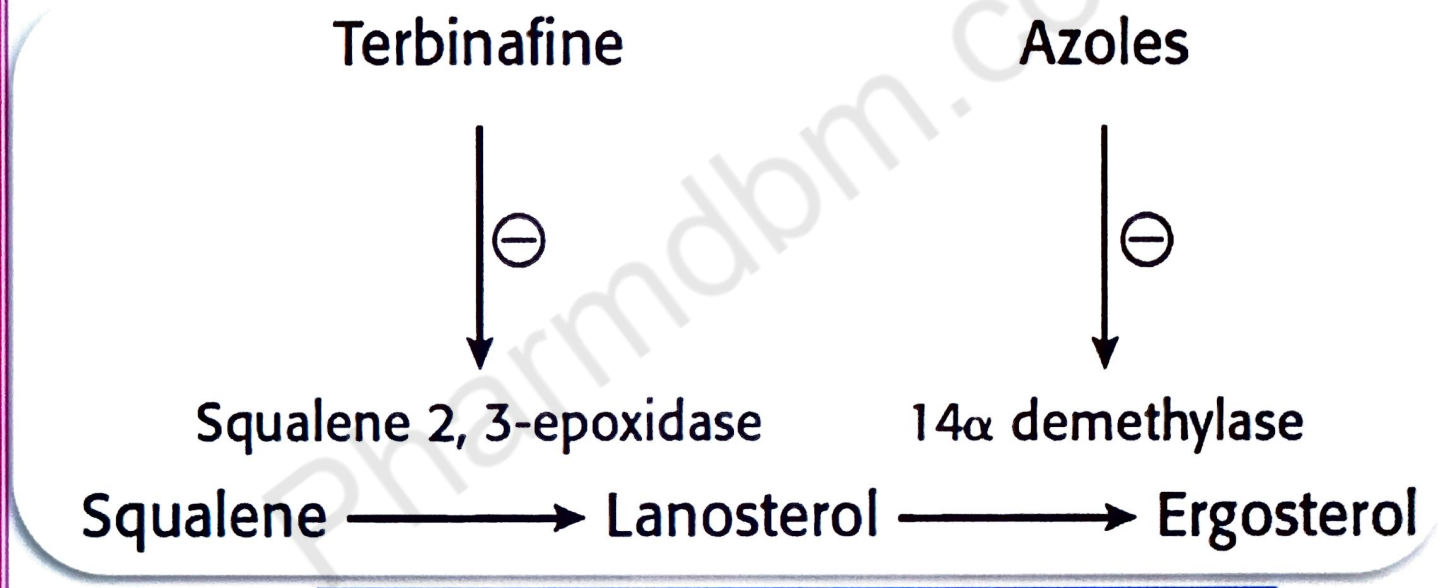
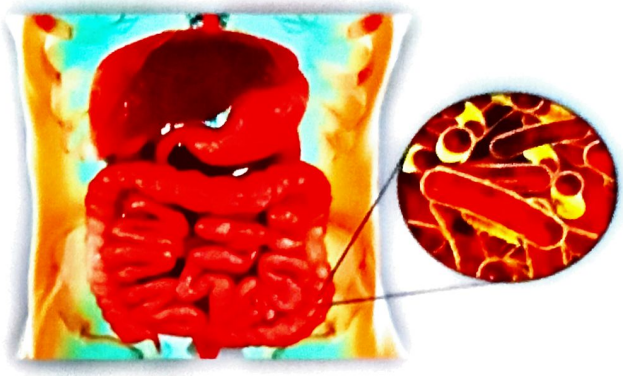


Fig :- Mechanism of action of terbinafine

❖ Pharmacokinetics

- It is available for topical as well as for oral administration.
- It is well absorbed after oral administration and is concentrated in skin, nails and adipose tissue.
- It is highly **bound to plasma proteins, poorly penetrates the BBB, metabolized in liver** and is **excreted in urine.**
- Terbinafine is a **fungicidal agent.**

❖ Adverse effects



- Nausea
- Diarrhoea
- Dyspepsia
- Hepatitis
- It may cause **itching** , **rashes** , **local irritation** on topical use.

❖ Uses

1. Dermatophytosis

- Terbinafi ne is very effective **against dermatophytes.**
- It is used topically or orally for ***T. pedis, T. corporis*** **and** ***T. cruris.***
- In onychomycosis of **hands** and **feet**
- it is used orally and is more effective than **itraconazole.**

2. Candidiasis : Terbinafi ne is less effective in ***Candida*** **infections.**

V. Other topical agents

Other topical agents :- **Tolnafate , Undecylenic acid , Benzoic acid , Ciclopirox olamine ,Butenafine**

i. Tolnafate

- It is an effective drug for **tinea cruris** and **tinea corporis**, and most cases respond In 1–3 weeks.
- Because of poor penetrability it is **less effective in tinea pedis** and other **Hyperkeratinized** lesions.
- It is ineffective in **tinea capitis** (involving scalp) and **tinea unguium** (involving nails).
- Tolnaftate causes little irritation, but is inferior in efficacy to imidazoles.
- It is not effective in candidiasis or other types of superficial mycosis.

ii. Undecylenic acid

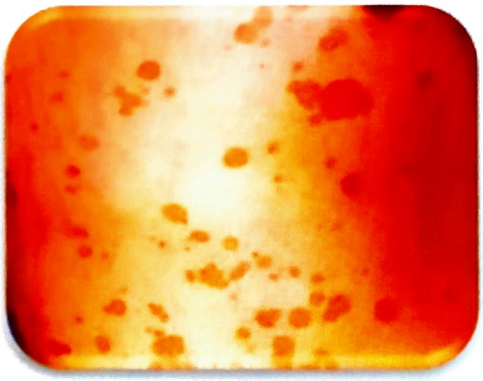
- It is **fungistatic** used topically,.
- Generally in combination with its **zinc salt**.
- It is still used for **tinea pedis**, **nappy rash** and **tinea cruris.**
- **Irritation** and **sensitization** are infrequent.

iii. Benzoic acid

- It has week **antifungal** and **antibacterial** property in slightly acidic medium.
- it is used in combination with **salicylic acid** (as Whitfield ointment: **benzoic acid 5%** or **6%** + **salicylic acid 3%).**
- The latter, by its **keratolytic action**, **helps to remove the infected tissue** and promotes the penetration of benzoic acid into the lesion. **Irritation** and **burning sensation.**

➢ **Whitfield's ointment:**

- ✓ It **contains 6% benzoic acid and 3% salicylic acid.**
- ✓ Salicylic acid has keratolytic and benzoic acid has **fungistatic effects**.
- ✓ It is used in the treatment of ***T. pedis.***



iv. Ciclopirox olamine

- It is a newer drug effective in tinea infections, **pityriasis versicolor** and **dermal candidiasis.**
- It penetrates superficial layers and reaches **hair roots** but **systemic absorption** is Negligible.
- Local tolerance without irritation is good.
- Sensitization occurs occasionally.

- Formulated **as nail lacquer** (painted like nail polish),
- It has been used in **onychomycosis,** but cure rate is low.
- Vaginal candidiasis can be treated by **1% ciclopirox vaginal cream .**

v. Butenafine

- It is a **benzylamine** congener of **terbinafine** with the same mechanism of action.
- However, it is used only topically in **dermatophytosis.**
- Efficacy in **tinea cruris/ corporis/pedis** is similar to that of topical terbinafine.