



“An Overview of Antifungal Agents: Classification, Mechanism of Action and Uses”

Dnyaneshwar Pawar^{*1}, Yuvraj Chavan^{*2}

Department of Pharmacology, Mahadev Kanchan college of Pharmaceutical Education and Research, Uruli kanchan, Pune

Address for Correspondence:

Dnyaneshwar Pawar*

E-mail-Id: dnyaneshwarpawar9933@gmail.com

How to Cite this Article:

Pawar, D. & Chavan, Y. (2026). An Overview of Antifungal Agents: Classification, Mechanism of Action and Uses. International Journal of Creative and Open Research in Engineering and Management, <i>02</i>(9), 1-9.
<https://doi.org/10.55041/ijcope.v2i9.184>

License:

This article is published under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

© The Author(s). Published by International Journal of Creative and Open Research in Engineering and Management.



OPEN ACCESS



<https://doi.org/10.55041/ijcope.v2i9.184>

ABSTRACT

Fungal infections represent a growing global health challenge, particularly with the rising population of immunocompromised patients, increased use of invasive medical procedures, and widespread antimicrobial resistance. Mycoses range from superficial infections of the skin and mucous membranes to severe, life-threatening systemic diseases. The limited number of selective antifungal targets, drug-related toxicity, delayed diagnosis, and the emergence of resistant fungal strains complicate effective management of these infections.

Antifungal agents play a crucial role in the prevention and treatment of fungal diseases by targeting unique components of fungal cells such as ergosterol, β -glucan, chitin, and nucleic acid synthesis pathways. This review provides a comprehensive overview of antifungal drugs, focusing on their classification, mechanisms of action, pharmacological properties, clinical applications, and limitations. Major classes discussed include polyenes, azoles, antimetabolites, allylamines, echinocandins, and topical antifungal agents.

The review also highlights important challenges in antifungal therapy, including drug resistance, toxicity, limited spectrum of activity, and

diagnostic delays. Recent advances in antifungal drug development, novel formulations, and emerging therapeutic strategies are briefly discussed to address these challenges. Overall, this review aims to provide pharmacy students and healthcare professionals with a clear and systematic understanding of antifungal agents and their role in improving patient outcomes in fungal infections.

KEYWORDS :-

Antifungal agents, mycoses, azoles, polyenes, echinocandins, antifungal resistance, mechanism of action, clinical applications



ANTI-FUNGAL DRUGS

INTRODUCTION : - A class of eukaryotic microorganisms known as fungus can cause systemic, cutaneous, subcutaneous, or superficial diseases. Fungi have microtubules made of tubulin, chitinous cell walls, and plasma membranes with ergosterol and 80S rRNA. This term "fungal infection" refers to the phenomenon of fungus having detrimental effects.^[1]

Primarily only two human diseases—or rather, disease complexes—caused by fungi were widely acknowledged until the middle of the nineteenth century. These were known as thrush (white, creamy patches on the tongue, cheeks, or throat) and ringworm since the Roman era. Fungal infection also known as mycosis.^[2] Before 19th period the people know that the ringworm is caused by some kind of parasitic worm due to these it is known as ringworm.^[3] According to current estimates, there are well over 100,000 species of fungi, and many more have yet to be identified, let alone categorized. Toadstools are examples of huge, multicellular fungi. But the majority of species are tiny, single-celled creatures and are most well-known as industrial agents (yeast fungus used to make bread and beer) and as medicinal agents (*Penicillia* spp. continue to be the source of the most often used antibiotic in the world). While tiny fungi, like yeasts, are single-celled microorganisms, larger fungus grow as microscopic filaments called hyphae that branch and expand into networks or colonies called mycelia.^[4]

SOME MOST COMMON FUNGI :-

The most common fungus is *Candida albicans*. This *C. albicans* works as symbiotic fungi when the immunity is healthy and its change into pathogenic condition this bacteria works with the pathogens for mutual interests. Additionally, *Candida albicans* can produce the perfect environment for other bacteria to live and colonise; these coinfections can result in more serious infectious disorders and medication resistance.^[5]

The most frequent cause of dermatophytosis in the world, *Trichophyton rubrum*, mostly infects human feet, skin, and the spaces between fingernails. One of the most well-known anthropophilic species of dermatophytes is *T. rubrum*, a fungus that frequently causes skin conditions and comes in a variety of white, yellow, brown, and red hues. Additionally, it can have a variety of textures, such as smooth, cottony, or waxy. Despite being often seen, *T. rubrum* infections are quite challenging to identify and distinguish from other dermatophytes. The identification of this fungal pathogen's genetic structure should drastically lower the medical expenses incurred by individuals who experience different types of dermatophytosis brought on by *T. rubrum*.^[6]

Aspergillus fumigatus is a common saprotrophic fungus means that it will feed on dead animals, plants or organic matter that is crucial to the recycling of carbon and nitrogen on Earth, it may also be a deadly opportunistic lung pathogen.

Furthermore, *A. fumigatus*'s cell wall possesses special characteristics that not only enable the fungus to endure in hostile conditions but also significantly influence its interactions with the mammalian immune system.

Cryptococcus neoformans is another fungi which causes disease cryptococcosis which primarily affect the patients having immunodeficiency (T cell deficiency) such in case of AIDs and HIV. The capsule and melanin synthesis are two phenotypic traits of *Cryptococcus neoformans* that have a significant impact on the virulence of the yeast since they both have protective properties and cause host harm.^[8] The primary habitats consist of garbage surrounding pigeon roosts and dirt contaminated by decomposing pigeon or chicken manure.^[9]

Candida auris is a newly discovered multidrug-resistant yeast that can spread in hospital environments, produce invasive infections, and have a high death rate. The earliest description of this yeast in 2009 and has since been documented in more than 20 nations across five continents.

There are various reasons why *C. auris* is a concern to global health

- i. Treatment options are extremely limited because multidrug resistance is prevalent and some isolates are resistant to all three major classes of antifungal medications.
- ii. In clinical laboratory, *C. auris* is frequently misdiagnosed.

Cases of *C. auris* may go unnoticed unless laboratories are aware of potential misidentification and have the capacity to do additional testing.^[10]



PREFACE OF ANTIFUNGAL AGENTS :-

Historical Perspective The field of antifungal chemotherapy is presently moving gradually, which began in 1903 with successful use of potassium iodide. There was little progress for the next half-century when nystatin was introduced in 1951, the first useful polyene antibiotic. Seven years later amphotericin B followed, which is still considered as the gold standard against which new systemic antifungals are compared. In 1959, M J Thirumalachar discovered hamycin from *Streptomyces pimprina* at Hindustan Antibiotics in India. Except for the development of flucytosine, there was again little progress until early 1970s when azoles came into existence.

Modifications of azole drugs, began with ketoconazole and some other agents those can be given orally as well as have increased potency, decreased toxicity with broader spectrum of activity. Fluconazole is another broad-spectrum triazole, came in clinical practice in 1990, has been shown to be efficacious in various forms of candidiasis. Itraconazole, a broad-spectrum oral triazole came in clinical practice in 1993, has greatest advantage over imidazoles that it is active against aspergillosis and cryptococcosis, though it is efficacious against endemic mycoses as well. The present era, which is characterized largely by modifications of azole drugs, began with ketoconazole and some other agents those can be given orally as well as have increased potency, decreased toxicity with broader spectrum of activity. Fluconazole is another broad-spectrum triazole, came in clinical practice in 1990, has been shown to be efficacious in various forms of candidiasis. Itraconazole, a broad-spectrum oral triazole came in clinical practice in 1993, has greatest advantage over imidazoles that it is active against aspergillosis and cryptococcosis, though it is efficacious against endemic mycoses as well.

The recent developments of resistance to the azole derivatives and increased prevalence of deep fungal infections have re-emphasized value of amphotericin B. Recent studies have shown ways to ameliorate well-known toxicities of this drug. A new approach is devised to make a complex of drug with lipids or entrap it into liposomes. The three lipid-based preparations were approved for clinical use (i) amphotericin B lipid complex in 1995; (ii) amphotericin B colloidal dispersion in 1996 and (iii) liposomal encapsulated amphotericin B in 1997.

Therefore, keeping in view of increasing resistance and tolerability of drug in special circumstances like renal failure, lipid formulations and azoles are two mainstays for antifungal therapy. The latest azole approved was isavuconazole on March 6, 2015, mainly for invasive aspergillosis and mucormycosis.^[12]

WORLDWIDE IMPACT OF FUNGAL INFECTIONS :-

The review estimates that over 6.55 million are impacted by invasive fungal infections each year, including over 2.1 million with invasive aspergillosis, 1.8 million with chronic pulmonary aspergillosis, 1.5 million with a *Candida* bloodstream infection or invasive candidiasis, 500,000 with *Pneumocystis pneumonia*, and 194,000 with Cryptococcal meningitis, based on data from publications published between 2010 and 2023. Every year, these illnesses cause around 3.75 million deaths, of which the fungal disease is directly responsible for 2.55 million. Additionally, the research predicts that 11.5 million individuals suffer from fungal asthma each year, with 46,000 asthma fatalities directly attributed to fungal allergies and 92,000 asthma deaths associated to fungal allergies.^[11]

PRIMARY CHALLENGES IN FUNGAL TREATMENT :-

Clinically accessible antifungals restricted range of action, significant toxicity, and developing resistance limit their usefulness. Since fungi and their human host are eukaryotic, finding novel targets for antifungals has always been a difficult task in the field of antifungal drug research. First-in-class antifungals, new structures for a known target, formulation changes to commercial antifungals, and repurposed medicines are examples of novel antifungals in clinical development. The field is paying more attention to aromatherapy and membrane-interacting peptides. Antifungal antibodies are moving forward into clinical studies, making immunotherapy another intriguing therapeutic approach. Additionally, new targets for antifungal therapy are being found, which enables the development of new, promising drugs that might address the resistance problem.^[12]



The number of safe therapeutic targets is significantly limited because fungi and human cells share many biological pathways and structural characteristics. Since fungi are eukaryotic creatures as opposed to bacteria, the majority of their metabolic and biosynthetic processes are similar to those of the host. Only a few distinct fungal components, like ergosterol, β -glucan, and chitin in the cell wall, can be specifically targeted without endangering human cells due to this similarities. Treatment options are limited due to the modest range of antifungal medication classes resulting from the limited number of different targets. Drug resistance, toxicity problems, and a lack of flexibility in therapeutic decision-making are all consequences of this limitation.^[13]

Amphotericin B — one of the oldest and most effective antifungals — is well known for causing kidney damage and severe infusion reactions.

Azole drugs can interfere with liver enzymes, leading to liver toxicity and many drug interactions. Even the newer drugs, like echinocandins, are not completely free of side effects and may still cause liver enzyme abnormalities in some patients.^[14]

Traditional diagnostic methods — like culture — take a long time, sometimes more than a week, and some fungi do not grow well at all. Blood tests such as β -D-glucan and galactomannan are helpful, but they can give false results depending on other infections or medications. More advanced tests like PCR are faster and more accurate, but they are expensive, require trained staff, and are not available in many hospitals. Because of these delays, treatment often starts late, which increases the risk of complications and death, especially in invasive fungal infections.^[15]

PURPOSE AND SCOPE OF REVIEW : -

The prevalence of fungal infections is rising globally, but our available treatments have not kept up with this development. Infections that are difficult to identify, difficult to treat, or resistant to current medications continue to plague a large number of patients. As a result, there is a pressing need to compile our present understanding of antifungal medicines and the difficulties associated with their use.

This study aims to provide readers with a comprehensive and well-organised grasp of antifungal therapy, covering everything from the medications we currently use to the issues that restrict their efficacy. This overview describes how antifungal drugs function, where they fall short, and what novel strategies are being investigated to enhance treatment going forward.

This review's scope includes:

- An examination of the growing prevalence of fungal diseases worldwide and the reasons for the need for more effective treatments.
- A concise yet thorough description of the main kinds of antifungal medications and how they work against fungal cells.
- A review of the main therapeutic obstacles, such as toxicity, resistance, restricted medication targets, and issues in early diagnosis of fungal infections.
- A summary of emerging research avenues, including novel drug delivery methods, repurposed medications, and immune-based treatments.
- Determining existing knowledge gaps and potential areas for further study. The overall goal of this study is to provide readers with a comprehensive and understandable picture of antifungal medicines, enabling both professionals and students to better comprehend the advancements made thus far and the work still required to enhance patient outcomes.

Biology of Fungi

The Kingdom Fungi, which includes moulds, mushrooms, lichens, rusts, smuts, and yeasts, is made up of eukaryotes with astonishingly varied life histories that are vital to human industry, research, medicine, and the biosphere. We point out that many fungi have haploid genetics and that those in cultivation are practically immortal, two characteristics that make it easier to associate traits with genotype, even for complex traits, than with *Drosophila* or *Arabidopsis*, in an attempt to persuade biologists to include fungi in their research. With more than 100 completed genome sequences available, fungi have led the way as models for eukaryote genome sequencing because their normal genome size of 30–40 Mb is tiny by eukaryotic standards. DNA alterations, gene knockouts, and knockdowns are common for certain fungus.

Ascomycota and Basidiomycota species have distinct tissues and simple, multicellular growth. These tissues are large enough in many animals to enable laboratory and even natural studies of transcription and translation. A population of

aquatic, unicellular eukaryotes that produced sporangia with zoospores and a single posterior flagellum split into two branches approximately a billion years ago, give or take 500 million years. One of these lineages eventually gave rise to mammals, while the other gave origin to fungi.^[16]

By absorbing nutrients through their cell walls, fungi receive their carbon compounds from either live organic material (parasites) or nonliving organic substrates (saprophytes). Simple sugars and amino acids are examples of small

Structure of Fungal Cell with Diagram

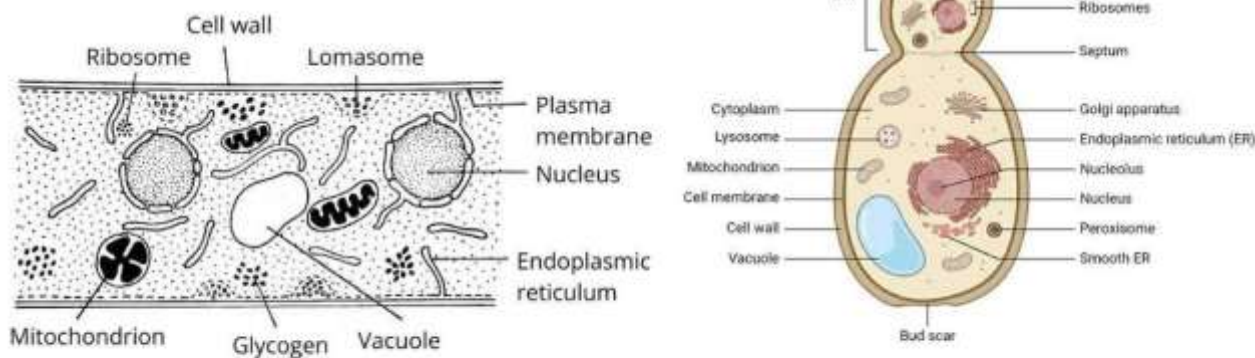


Figure 1 : Fungal cell

molecules that build up in a thin layer around the hyphae or yeast and then diffuse through the cell wall. Conversely, before being absorbed by the fungal cell, macromolecules and insoluble polymers (such as proteins, glycogen, starch, and cellulose) must first undergo digestion. This process includes the extracellular breakdown of the substrate or substrates, the release of certain proteolytic, glycolytic, or lipolytic enzymes from the hypha or yeast, and the diffusion of the digested products via the fungal cell envelope. These digestive enzymes are necessary for fungal pathogens to get past the host's natural defences.

CELL WALL :-Although not all fungal species have cell walls, the ultimate morphology of fungal elements is significantly influenced by cell wall formation in those that do. As a result, our understanding of fungal cell wall biosynthesis and fungal morphogenesis have developed simultaneously. Additionally, the fungal wall prevents harmful macromolecules from entering the cell and shields it from mechanical damage. This filtering function might be particularly crucial in shielding fungal pathogens from some of the host's fungicidal substances. Additionally, the fungal cell wall is necessary to stop osmotic lysis. Because of the protoplast's internal (turgor) pressure, even a tiny cell wall defect can cause cytoplasm to extrude. Fungal cell walls are composed of very simple materials, such as chitin, that are not commonly present in animal and plant hosts. Based on this, studies of the biosynthesis of fungal wall components may be able to discover pathogen-specific molecular targets. The development of antifungal medications that are safe for mammalian cells may depend heavily on these targets.

YEAST AND HYPHAL MORPHOGENESIS :-

At the tips, hyphal (the long, branching, thread-like filaments that form the body ([mycelium](#)) of most fungi) development takes place by extension. The directional migration and accumulation of vesicles that transport wall precursors and wall synthetases to the exocytosis location at the hypha's apical dome, at least in part, dictate this polarisation (Fig. 73-3). Ultrastructural studies have revealed a complex arrangement of tip-growth-related organelles and cytoskeletal components, despite the apparent simplicity of hyphal morphogenesis. There is proof that the apical dome of the hypha is where intussusception and polymerisation of chitin microfibrils take place, and that membrane-bound chitin synthetase activity regulates the manufacture of this important cell wall constituent. Microvesicles known as chitosomes have been found to contain the zymogen form of chitin synthetase, which seems to carry this enzyme to the hyphal tip. The chitosomes can form from Golgi-like entities or through the free self-assembly of subunits in the cytoplasm or bigger

vesicular bodies. When the chitosome fuses with the plasmalemma, chitin synthetase is activated. This could be the result of a membrane-bound protease interacting with the zymogen. At these fusion sites, chitin synthesis begins.

The orderly processes of hyphal tip extension and bud emergence depend on a balance between wall synthesis and wall lysis, or plasticization. It has been observed that the fungal wall contains lytic enzymes such as chitinase, N-acetyl- β -D-

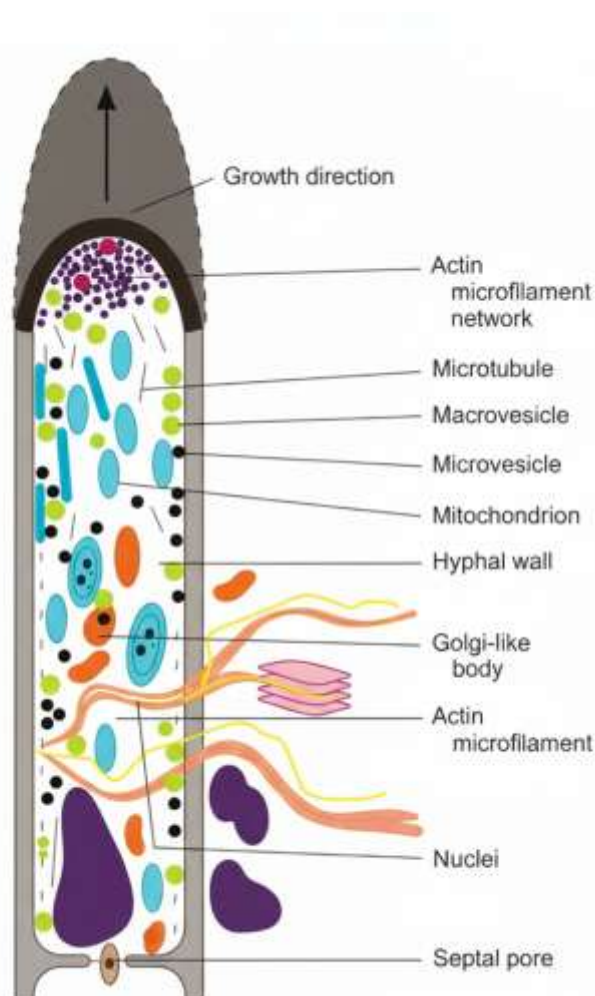


Figure 2 : Fungal cell growth

glucosaminadase, and β 1-3-glucanase. Macrovesicles may operate as a mediator in the localisation of such activity. Similar to microvesicles, these organelles are likely produced from Golgi-like entities and go to the hyphal tip or yeast bud, where they fuse with the plasmalemma to transport their contents to the wall synthesis site.

REPRODUCTION :-

In fungi, sexual reproduction generally involves meiotic division of the resulting diploid nucleus after the fusing of two haploid nuclei (karyogamy) . Sometimes the only way to make sexual spores is to fuse two nuclei of different mating types, which requires first conjugating distinct thalli. Heterothallism is the term for this sexual reproductive situation, while heterokaryosis is the term for the nuclear fusion. Karyogamy typically occurs fairly quickly after plasmogamy, which is the fusion of two hyphal protoplasts that brings the nuclei close together within the same cell. However, in other Basidiomycotina members, these two processes are spatially and temporally separated, with plasmogamy producing a pair of nuclei (dikaryon) inside a single cell. The fungus can delay karyogamy until much later in its life cycle. In the meantime, the binucleate cell grows and divides. The two closely related nuclei divide simultaneously and the sister nuclei split into two daughter cells to form a dikaryotic mycelium .Homothallism, in which a nucleus within the same thallus can fuse with another nucleus of that thallus (i.e., homokaryosis), is an alternate method of sexual reproduction in fungus. Investigations into fungal genetics require an understanding of these nuclear cycles.

Fungi can also be reproduce via asexually. These comprise the broad category of cylindrical fungi (like *Coccidioides immitis*) and asexual (imperfect) yeasts (like *Candida* species). The majority of people in this group are no longer able to make meiospores. these have uncommon sexual reproduction, and we may not yet know the sexual (ideal) stage for



these species. Apart from simple budding in yeasts, the most prevalent forms of asexual reproduction include blastic development of conidia from specialised hyphae (conidiogenous cells), fragmentation of hyphae into conidia, and conversion of hyphal elements into conidia or chlamydospores (thick-walled resting spores).

These imperfect fungus do not undergo meiosis during their life cycle, yet a process known as parasexuality allows for the recombination of genetic variation and inherited traits. The production of diploid nuclei in a heterokaryotic, haploid mycelium resulting from plasmogamy and karyogamy, the multiplication of diploid and haploid nuclei in the heterokaryotic mycelium, sorting out of a diploid homokaryon, segregation and recombination by crossing over at mitosis, and haploidization of the diploid nuclei are the main events of this process. There is no conflict between parasexual and sexual cycles. Certain sexually reproducing fungus also display parasexuality.^[17]

PATHOGENICITY AND VIRULENCE FACTORS OF FUNGI :-

ADHESION TO THE HOST- A fungal cell's cell wall gives it its form and serves several vital purposes, such as defence against environmental pressures. The biosynthesis and cell wall structure of *C. albicans*, baker's yeast, and a few other species have been extensively studied (15–20). The carbohydrates β -1,3- and β -1,6-glucan and chitin make up between 60 and 70 percent of the total cell wall mass in *Candida* species. Furthermore, a variety of glycoproteins are found in the cell walls of various fungus, including *Candida* species. Mannose residues added by N-glycosylation, O-glycosylation, and/or glycosylphosphatidylinositol (GPI) anchoring make up between 80 and 90 percent of the cell wall protein content in *Candida*.

Mannose residues added by N-glycosylation, O-glycosylation, and/or glycosylphosphatidylinositol (GPI) anchoring make up between 80 and 90 percent of the cell wall protein content in *Candida*. GPI proteins, which make up most of the cell wall proteins, are covalently attached to β -1,6-glucan by a remnant of their GPI anchor. Superoxide dismutases, aspartyl proteases, phospholipases, adhesins, and other proteins that control main host-pathogen interactions are among

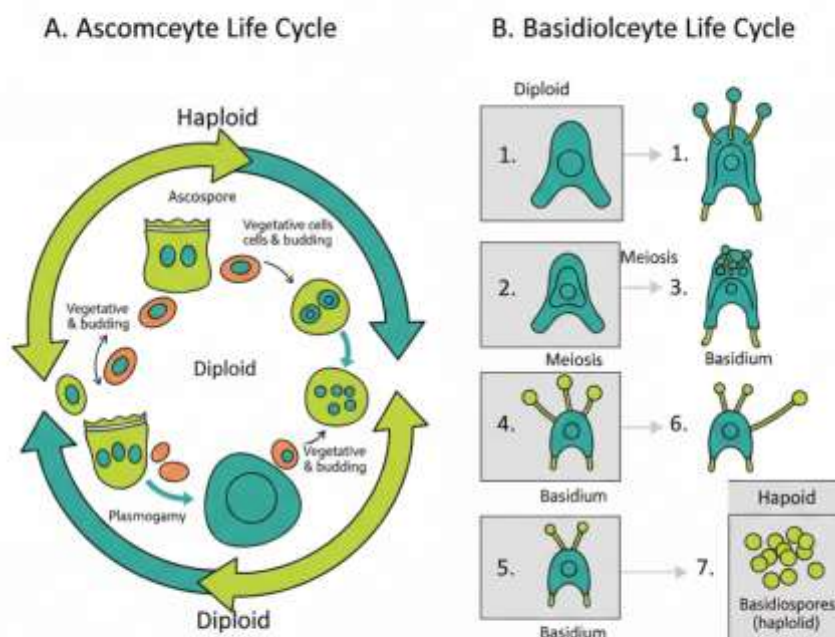


Figure 3: Fungal Reproduction

these proteins, which are primarily found on the outer portion of the cell wall.

GPI-modified wall proteins make up the majority of known fungal adhesins. Because conserved characteristics are present in the fundamental structure of GPI protein precursors, potential adhesins can be identified using bioinformatic



methods. They have a signal peptide for entry into the endoplasmic reticulum (ER) at their N terminus and a peptide for anchoring to a preformed GPI lipid in the ER membrane at their C-terminal end. Transmembrane domains are absent from mature GPI proteins. The majority of known mature adhesins are big proteins with a modular structure that typically contain more than 800 amino acids. Their very complicated N-terminal domain facilitates certain interactions between proteins, proteins and sugars, or other proteins and ligands.

These are thought to be primarily in charge of the particular interactions with their substrates, such as carbohydrates or proteins on the surface of the host cell.

It is succeeded by a variable, low-complexity domain that typically has tandem repeats (TRs) and is rich in serine/threonine (Ser/Thr). Due to slippage and/or recombination events during DNA replication, which result in the addition or removal of repeat units, the repeat regions are susceptible to large intraspecies length polymorphisms. Because the N-terminal effector domain is still buried in the cell wall, shorter repeat sections may result in reduced adhesion, whereas longer repeat regions may confer increased adherence. Adhesin binding specificities were primarily investigated using two complementary methods. Creating knockout mutant strains and examining their characteristics is the initial method for evaluating gene function. On the other hand, fungal adhesin genes frequently belong to multigene families. Functional redundancy and compensatory mechanisms that result in the overexpression of other Heterologously expressing entire or partial adhesins on the cell surface of *S. cerevisiae* for gain-of-function investigations is a successful alternate strategy to get around these issues. There are strains of *S. cerevisiae* that are very poorly adherent to most substrates because they do not have a functioning copy of the gene encoding the flocculin-regulating transcription factor Flo8. Thus, adherence to possible binding ligands mediated by the gene of interest can be evaluated using this method. For example, heterologous expression studies in *S. cerevisiae* shown that the proteins encoded by the EPA gene family mediate, at least partially, *C. glabrata* adhesion to epithelial and endothelial cells. Adhesion genes whose products have comparable or at least partially identical activities so frequently hinder this strategy. Furthermore, under the experimental settings commonly utilised in the laboratory, many adhesion genes only exhibit minimal levels of expression.

The study of fungal adhesins has recently shifted towards more structural investigations using nanotechnology. X-ray crystallography, nuclear magnetic resonance (NMR), and atomic force microscopy (AFM) are used to obtain detailed information about the structure and ligand-binding specificities of adhesins in *Candida albicans*, *Candida glabrata*, and *Candida cerevisiae* (called flocculins in the latter organism). Our knowledge of how fungal adhesins affect adhesion, aggregation, biofilm formation, and host-immune responses is undoubtedly much enhanced by these high-resolution techniques.^[18]

CELL WALL SYNTHESIS :- Cell wall of the fungi is the outer covering of the fungi. It contains various components like chitin, β -glucans, and mannoproteins which can become the targets of many antifungal agents. It leads to the study of this components essential to prepare potent antifungal agents

i) Chitin synthesis pathway :-

Chitin is a β -(1 $\rightarrow$ 4)-linked polymer composed of N-acetylglucosamine (GlcNAc). Despite making up a lesser percentage of the wall in yeasts, it is crucial for cell division, septum creation, and stiffness maintenance.

Synthesis of chitin begins in the cytoplasm of yeast.^[19,20]

ii) β -1,3-Glucan Synthesis Pathway :- Most crucial and most abundant component from the cell wall of fungi.

iii) Mannoprotein forms outermost layer of the fungi. It involves the environmental sensing, adhesion to host, immune invasion. Targeting these pathways leads to the designing the effective antifungal agent.

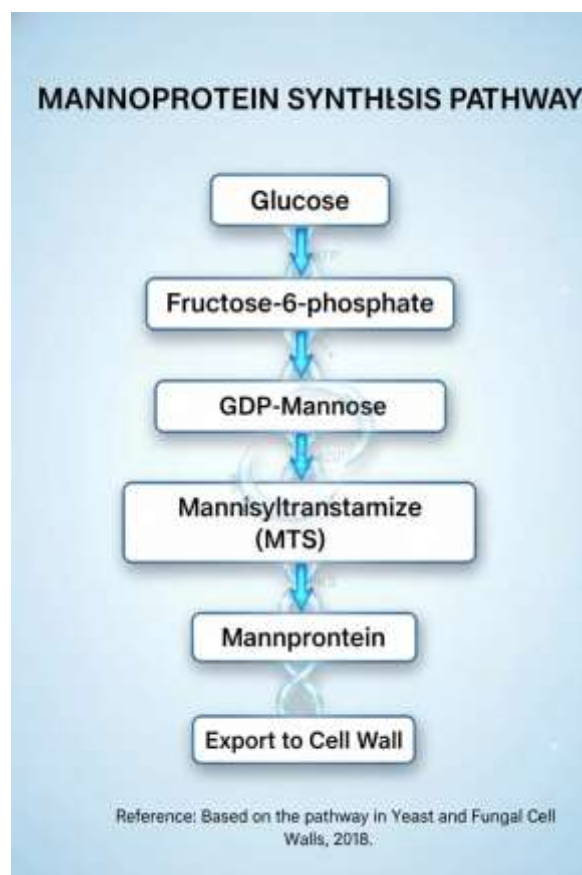
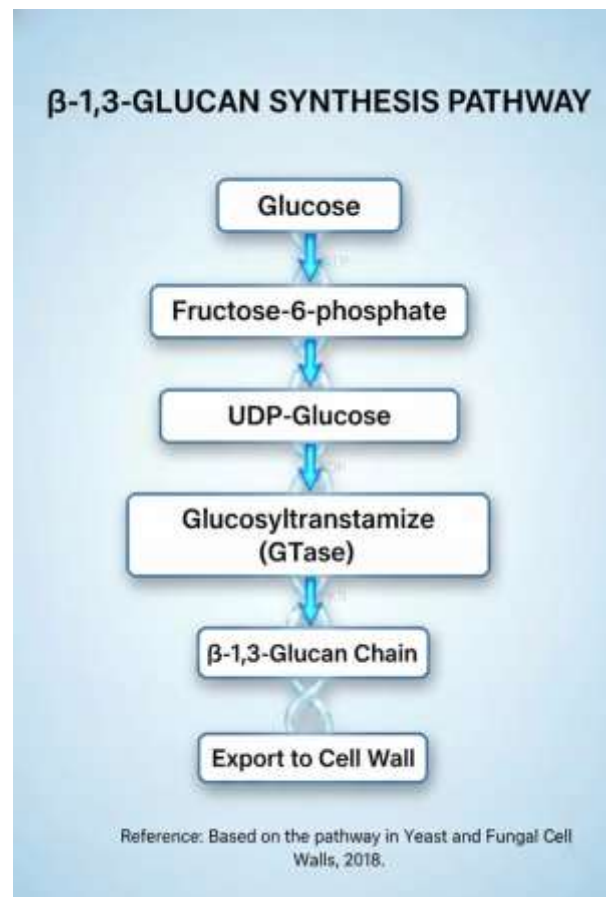
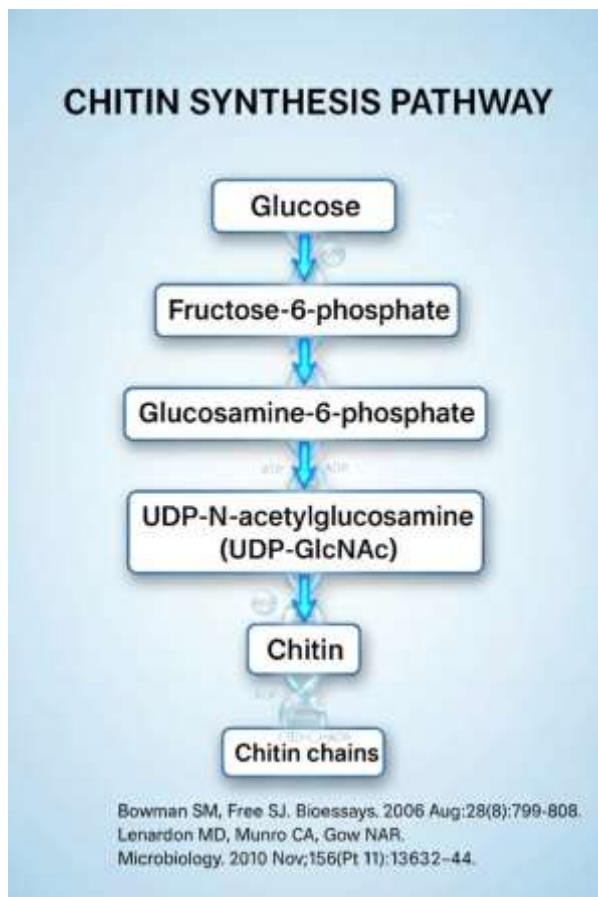


Figure 4: Fungal cell important nutrients

CLASSIFICATION OF ANTIFUNGAL AGENTS

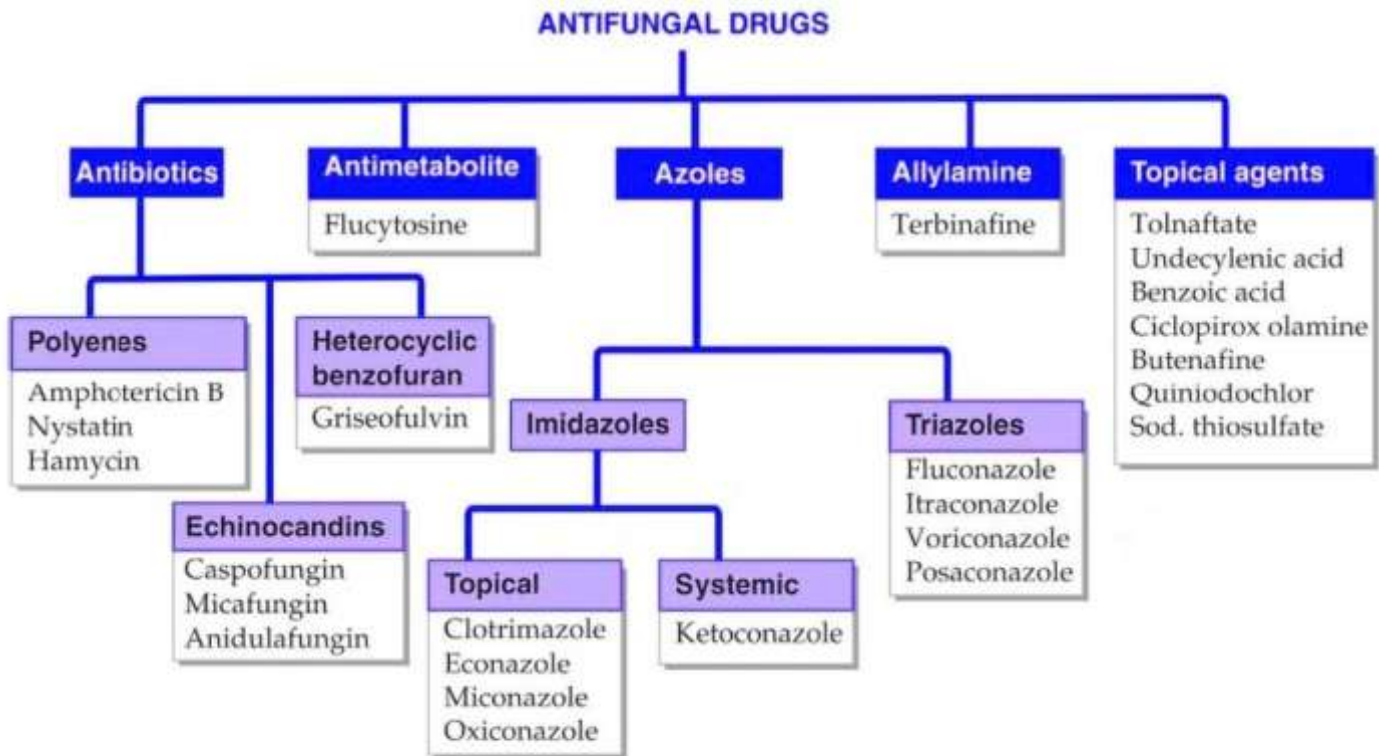


Figure 5: Antifungal agents classification chart



POLYENES :-

Polyenes like nystatin, amphotericin B, and pimaricin attach to sterol components in the phospholipid-sterol membranes of fungus cells to create complexes that alter the membrane's structure. A polyene macrolide's affinity for various sterols in fungal cell membranes is influenced by its molecular size and number of conjugated links. Compared to eukaryotic (host) cell membrane cholesterol, amphotericin B has a higher affinity for fungal ergosterol, the primary sterol in fungal membranes. The fungal cell membrane develops channels as a result of the lengthy polyene structure.

Critically crucial molecules are lost as a result of the membrane's permeability being reduced. Internal acidification and a stop to enzymatic activities are brought on by hydrogen ion influx and potassium ion efflux from the fungal cell. An arrested cell will eventually release sugars and amino acids. At typical polyene concentrations, fungistatic effects are typically noticeable. Fungicidal rather than fungistatic effect may result from high medication concentrations and pH levels in the surrounding medium between 6.0 and 7.3.

NYSTATIN

In 1949, while working at the New York State Department of Health's Division of Laboratories and Research. It comes from *Streptomyces noursei*. Slome noted in 1955 that topical nystatin was especially useful for treating noninvasive candidiasis, a common side effect seen in children participating in early chemotherapy leukaemia studies. Nystatin showed modest action against *Aspergillus* species and good activity against *Candida*. Nystatin clumps in aqueous solutions that are harmful to mammalian cells both in vivo and in vitro.

Its toxicity and insolubility prevented it from being used as an intravenous treatment for systemic mycosis. Nystran, a more soluble liposomal nystatin formulation with lower toxicity, was recently created. The liposomal formulation is made up of a freeze-dried, solid nystatin dispersion combined with a dispersing agent, like polysorbate or poloxamer. The dispersing agent increases the drug's solubility and reduces toxicity while preserving efficacy by preventing aggregation formation in solution. In vitro, liposomal nystatin exhibits strong effectiveness against a range of *Candida* species, including isolates that are resistant to amphotericin. Unfortunately, significant infusion-related toxicity stopped the development of this medication even though the liposomal form of nystatin was less toxic than traditional nystatin.

AMPHOTERICIN B

The primary antifungal medication used to treat life-threatening mycosis and the majority of other mycosis, possibly excluding dermatophytosis.

This medication attaches itself to the membrane sterols of fungal cells, impairing their ability to function as a barrier and causing cell constituents to be lost. Membrane changes result in cell death and metabolic disturbance.

Research on the sterol content of mutant strains of *Cryptococcus neoformans* and *Candida albicans* has shown that resistance is frequently linked to changes in the sterol composition of the membrane. Its wide range of activity encompasses the majority of medically significant moulds and yeasts, including dimorphic pathogens like *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Paracoccidioides brasiliensis*. It was discovered by Gold in 1956 and can be considered a gold standard.

This antifungal medication is the preferred treatment for the majority of opportunistic mycoses brought on by fungus like *Aspergillus* species, *Candida* species, *Cryptococcus neoformans*, and zygomycetes. Although amphotericin B resistance is uncommon, it is notable for *Pseudallescheria boydii*, *Fusarium* species, and *Trichosporon* species. The medication must be given intravenously and has a number of adverse effects, from chills and phlebitis at the infusion site to potentially serious kidney damage. Understanding the mechanism of this agent's renal toxicity—which is thought to entail tubuloglomerular feedback—has led to a significant advancement in its use. Sodium chloride administration may lessen the inhibition of glomerular filtration.



NATAMYCIN

The naturally occurring antifungal compound natamycin, often called pimaricin and occasionally marketed as Natacyn, is created during fermentation by the soil-dwelling bacterium *Streptomyces natalensis*. Despite its extremely low water solubility, natamycin is effective at relatively low concentrations. For the majority of moulds, the minimum inhibitory concentration (MIC) is less than 10 ppm. Natamycin is a medication used to treat fungal keratitis, an infection of the eye, and is categorised as a macrolide polyene antifungal. By binding selectively to ergosterol, natamycin inhibits the growth of fungi through a unique method of action. It works particularly well against corneal infections caused by *Aspergillus* and *Fusarium*.^[21]

GRISEOFULVIN

Fungal RNA is bound by the phenolic, benzofuran cyclohexane antifungal drug griseofulvin. It was the first antifungal agent created as a systemic plant protectant and is a byproduct of *Penicillium janczewskii* fermentation.

It interferes with DNA synthesis by acting as a strong thymidylate synthetase inhibitor. It also inhibits the production of chitin, a crucial part of the fungal cell wall, and damages fungal microtubules. The clinical use of griseofulvin as an oral medication for treating human dermatophyte infections (skin, nail, and hair infections) has declined since the introduction of more recent antifungal medications like terbinafine and itraconazole. Nonetheless, it is still commonly advised in veterinary practice for treating equine sporotrichosis and small animals like dogs and cats.^[22]

MECHANISM OF ACTION :-

In general, polyenes work differently from other antifungal medication families because they interact with ergosterol, a crucial chemical, rather than a particular enzyme. In 1958, Gottlieb et al. published the first evidence of the mechanism of action of polyenes when they found that the fungicidal effect of nine polyenes, including filipin, AmB, and nystatin, on three fungal species could be inhibited by the addition of sterols like cholesterol, lanosterol, and ergosterol. They proposed that polyenes may either competitively replace the sterols as a cofactor of a key metabolic reaction or inhibit the synthesis of sterols, as the then-undiscovered azole, allylamine, and phenylmorpholine antifungals do.

However, it was later shown that polyenes can react with sterols to change the membrane's permeability. It is still up for discussion how this sterol sequestration process operates. The pore-forming concept, in which polyenes interact with ergosterol to create ion-leaking pores in the membrane, is the most researched mechanism of action. However, it has been demonstrated that pore formation can occur even in the absence of sterols. Early research by Cotero et al. suggested that sterols may not be directly involved in pore creation, but they are crucial for the membrane's structure during amphotericin activity. Subsequent research confirmed this theory. For instance, it has been demonstrated that the polyene natamycin can bind ergosterol without changing the permeability of cell membranes.

Additional investigation revealed that natamycin disrupts vital cellular functions like glucose transport, amino acid transport, and vacuolar fusion by inhibiting a number of ergosterol-dependent membrane proteins. The pore forming model, the surface adsorption model, the sterol sponge model, and the oxidative damage model are the four models of the polyene mode of antifungal activity that have now been put forth.

The polyene's ability to bind to ergosterol is essential to its antifungal action in all suggested models. Numerous fungal biological functions, such as the control of membrane proteins, endocytosis, cell division, membrane fluidity, and cell signaling, depend on ergosterol. Because ergosterol has a very different three-dimensional structure from mammalian cholesterol, therapeutic polyenes are specific to ergosterol. This allows ergosterol to better bind into the hydrophobic "pocket" of polyenes like AmB, as shown in The binding of AmB and ergosterol is influenced by three interdependent forces: Van der Waals forces, which are greatest when both molecules are parallel and co-planar, a network of hydrogen bonds between the sterol's 3 β -OH group and AmB's polar mycosamine group, as well as π - π electronic interactions between the ergosterol side chain and AmB's polyene "tail." When AmB binds to cholesterol, the latter crucial "attach point" is not reached. Furthermore, because the sterol side chain has a sigmoidal shape, Van Der Waals interactions between cholesterol and AmB are weaker. The selectivity of most polyenes to fungal cells is explained by the specific



binding and the higher ergosterol:phospholipid ratio in fungal cell membranes compared to the cholesterol:phospholipid ratio in human cells.

PORE FORMING MODELS :-

The pore formation concept, in which polyenes and ergosterol combine to produce an ion channel-like complex that leaks ions and small organic molecules from the cell and ultimately causes cell death, is the most researched model of polyene activity. Because polyenes are amphipathic, they would orient themselves in the plasma membrane with their hydrophilic polyol portion forming an aqueous channel and their hydrophobic polyene "tail" interacting with ergosterol, directed to the inner lipid environment of the membrane, as shown in Figure 3A,B. This channel is further stabilized by intermolecular hydrogen interactions between the amino and carboxyl groups of the hydrophilic "heads" of nearby polyene molecules. Such an architecture can arise when AmB interacts with ergosterol, according to neutron diffraction research.

A pore is usually formed by four to twelve polyene monomers. Two types of channels can be created because the average length of AmB is nearly equal to the length of a membrane phospholipid: a "half-pore" with only one polyene ring and a full pore with two ring complexes of polyenes. Although the structures of both types are nearly identical, the latter would cause the lipid bilayer to thin conformationally.

The polyene and the membrane's composition and thickness would largely determine which pore forms. For instance, in a membrane mostly made of dimyristoylphosphatidylcholine (DMPC), AmB would mainly generate half-pores. Only when a specific threshold of polyene molecules in the membrane is met do pores form. True pores and half-pores can also carry bigger nonelectrolyte molecules, however aggregate complexes known as "non-aqueous pores" or "cation-selective pores" can improve the membrane permeability to monovalent cations below this threshold. Compared to membranes containing cholesterol, this threshold is substantially lower (by a factor of five to ten) in membranes containing ergosterol.

Additionally, patch clamp experiments using synthetic AmB channels have demonstrated its antifungal specificity by demonstrating that ion transport happens more quickly (a shorter channel "dwell time") in ergosterol-containing membranes than in cholesterol-containing membranes. Sterol type and concentration have no effect on the selectivity of transport or "leakage" out of the cell; instead, the diameter of the pore is determined by the type and concentration of polyene. The study by Yang et al. demonstrates this, showing that when the concentration of AmB multiplies by 40 in an ergosterol-rich membrane, the channel diameter increases 100-fold. Generally speaking, nystatin forms smaller pores (about 0.36 nm), but AmB forms rather wide pores (about 0.46 nm) and may transport molecules as large as sucrose.^[23]

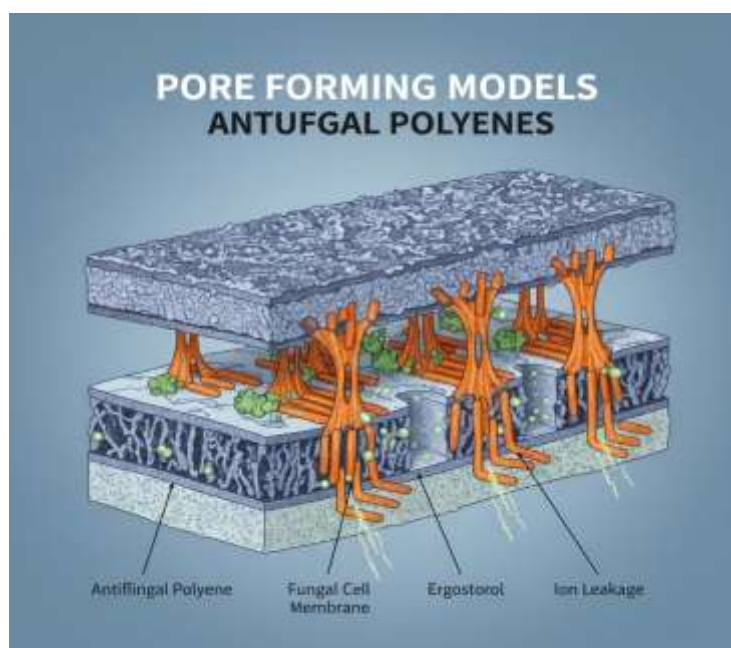


Figure 6: Functioning of

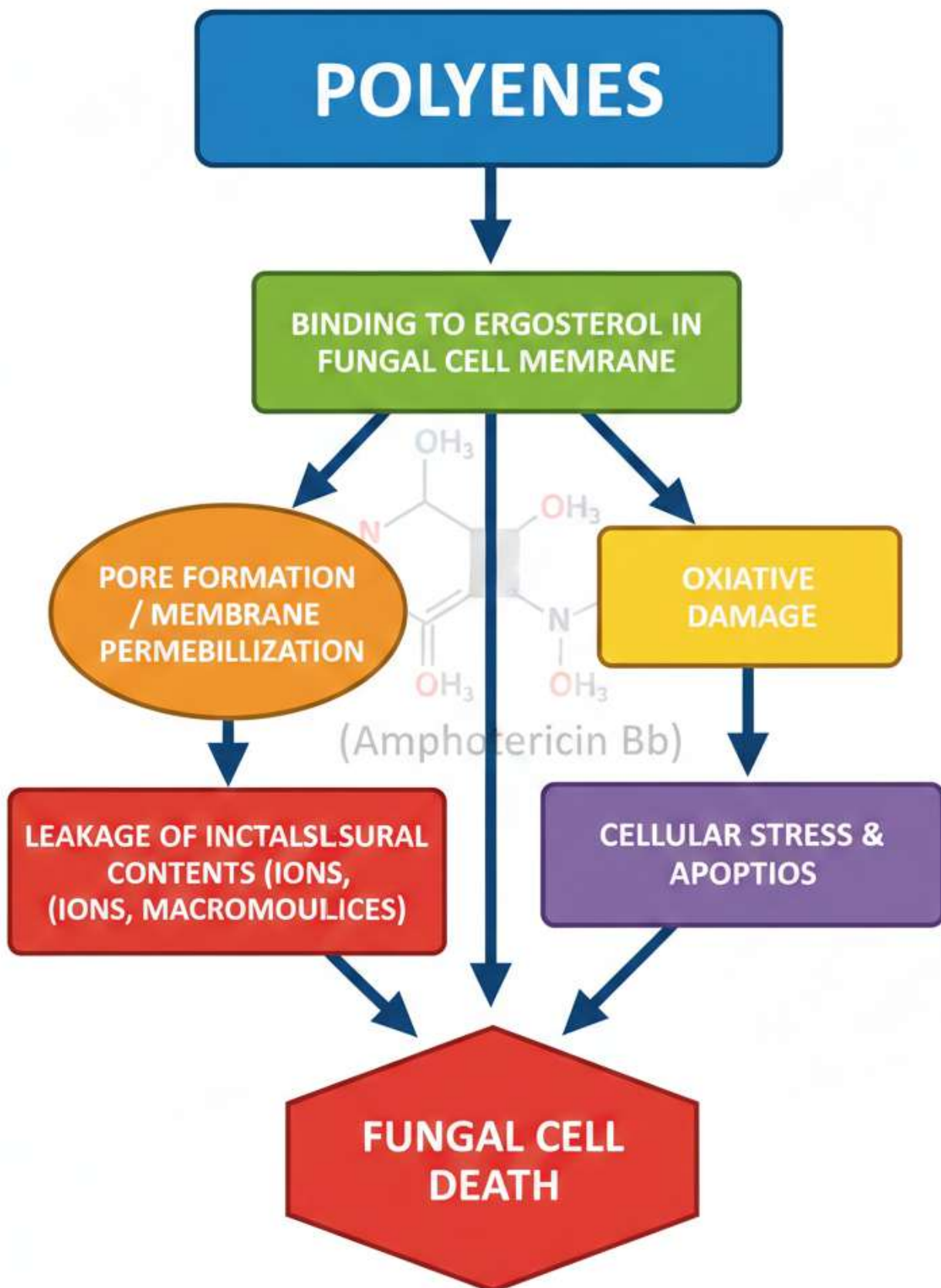


Figure 7 :MOA of polyenes



AZOLES

Imidazoles and **triazoles** are examples of azole antifungal drugs with five-membered chemical rings that include two or three nitrogen molecules, respectively.

The three imidazoles that are clinically beneficial are ketoconazole, miconazole, and clotrimazole. Itraconazole and fluconazole are two significant triazoles. The cytochrome P450-dependent enzyme involved in the formation of cell membrane sterols is believed to be inhibited by all azole antifungal drugs. The oral antifungal azoles were made possible by ketoconazole. It is widely used in nonimmunocompromised people to treat infections caused by *Histoplasma capsulatum* and *Blastomyces dermatitidis*. It can be either locally or orally.

Additionally, it is effective against a range of cutaneous mycosis, including dermatophyte infections, pityriasis versicolour, and cutaneous candidiasis, as well as mucosal candidiasis. It is not recommended for the treatment of systemic infections brought on by yeasts or aspergillosis.^[24]

A) IMIDAZOLES WITH FUSED RINGS :-

A cyclic five-member ring with three carbon and two nitrogen molecules makes up the fundamental imidazole structure. Two carbon molecules and a fused benzene ring are shared by the fused-ring imidazoles. Two of these substances have minimal antifungal activity, but the majority have parasitic (anthelmintic) activity: Thiabendazole with 1-chlorobenzyl-2-methylbenzimidazole.

1) 1-2-methylbenzimidazole chlorobenzyl

The azole 1-chlorobenzyl-2-methylbenzimidazole was created especially to combat *Candida*. It has previously been used to treat dermatophytic infections and superficial yeast.

2) Thiabendazole

Thiabendazole has a limited effect on dermatophytes and was created as an anthelmintic. In the past, it was also used to treat dermatophytic infections and superficial yeast. Dogs with penicillosis and aspergillosis have been treated with thiabendazole.

B). MONO-N-SUBSTITUTED IMIDAZOLES :-

This group has one of the two nitrogen molecules substituted while the imidazole ring remains intact. For use in agriculture and medicine, at least three series of these chemicals have been developed. The nonsymmetrical carbon atom connected to one nitrogen molecule of the imidazole ring undergoes replacements in the tri-phenylmethane series. In the second series, the nitrogen molecule is substituted at a phenethyl configuration. Instead of the 1-phenethyl molecule, the dioxolane series is based on a 1,3-dioxolane molecule. The range, particular degree of antifungal activity, administration methods, and possible applications of each series differ.

1.CLOTTRIMAZOLE :-

The first clinically significant member of the triphenyl-methane series is clotrimazole. At very low concentrations, it exhibits good in vitro action against a wide range of fungi, including moulds and yeasts. However, its use has been restricted to topical applications (1% cream, lotion, solution, tincture, and vaginal cream) for superficial mycoses (nail, scalp, and skin infections) caused by dermatophytes and *M. furfur*, for initial and/or mild oropharyngeal candidiasis (OPC; 10-mg oral troche), and for intravaginal therapy (single application of 500-mg intravaginal tablet) of vulvovaginal candidiasis due to hepatic enzymatic inactivation. Applications of other intravaginal medications take three to seven days. Additionally, this medication is used to treat nasal aspergillosis (fed through tubes), dermatophytic infections, and candidal stomatitis in dogs.



2.ECONAZOLE, ISOCONAZOLE, OXICONAZOLE, AND TIOCONAZOLE :-

Other frequently used topical imidazoles include econazole (1% cream), isoconazole (1% cream), oxiconazole (1% cream and lotion), and tioconazole (6.5% vaginal ointment). As with clotrimazole, a single application of tioconazole is effective in the management of vulvovaginal candidiasis and as a nail lacquer for fungal onychomycosis (nail infections). Mild to moderate vulvovaginal burning has been associated with intravaginal therapy. Oxiconazole and econazole are less effective than terbinafine and itraconazole in the treatment of onychomycosis and other infections caused by the dermatophytes. Although topical agents do not cure onychomycosis as oral drugs do, they may slow down the spread of this infection. However, the recommended drugs for the treatment of onychomycosis are terbinafine (by dermatophytes) and itraconazole.

3.LANOCONAZOLE :-

Lanconazole has been used topically to treat dermatomycoses in recent years. Compared to prior compounds, it seems to have better activity in vitro and in experimental infections in guinea pigs.

5.Miconazole:-

The first azole derivative to be given intravenously to treat systemic fungal infections was miconazole. Its usage is restricted to specific cases of invasive infections brought on by the opportunistic mould *P. boydii* because of its toxicity and high relapse rates. This chemical was dissolved in polyethoxylated castor oil for systemic delivery because it is insoluble in water. The majority of miconazole adverse effects (pruritus, headache, phlebitis, and hepatitis) seem to be caused by this solvent. However, miconazole is used to treat aspergillosis in raptors, fungal keratitis and pneumonia in horses, dermatophytic infections in big animals, and nystatin-resistant yeast infections in dogs. Nevertheless, there is a lack of safety and effectiveness information (veterinary use).

C) TRIAZOLES :-

Due to the substitution of the triazole ring for the imidazole ring, the triazoles are characterised by a more specific binding to the cytochromes of fungal cells than to mammalian cells. Other advantageous effects include an enhanced resistance to metabolic degradation, an increased potency, and (i) a superior anti-fungal activity. Despite the fact that only three triazoles are presently approved for use in antifungal systemic therapy—fluconazole, itraconazole, and voriconazole—many more triazoles are undergoing varying degrees of clinical testing. In Europe, voriconazole has a licence.

1.FLUCONAZOLE :-

Fluconazole is a comparatively small molecule that is mostly eliminated as an active medication in the urine, somewhat soluble in water, and minimally attached to proteins. It has a lengthy half-life (up to 25 hours in humans) and effectively penetrates the CSF and parenchyma of the brain and the eye. The pharmacokinetics are linear and unaffected by the medication formulation or the mode of administration. When taken orally, fluconazole is well absorbed (total bioavailability exceeds 90%) and is unaffected by food or stomach pH. In healthy individuals, plasma concentrations of 2–7 µg/ml are typically measured following equivalent single doses of 100 and 400 mg. The peak plasma levels following several doses are 2.5 times greater than those following a single dose. In both healthy humans and lab animals, the CSF to serum fluconazole concentrations range from 0.5 to 0.9%. The majority of moulds are not susceptible to the in vitro or in vivo effects of fluconazole. Fluconazole is available in both oral and intravenous forms for the treatment of mucosal candidiasis (oral, vaginal, and esophageal), chronic mucocutaneous candidiasis in individuals of all ages, and candidemia in nonneutropenic and other nonimmunosuppressed patients. Currently, the preferred medication for maintenance treatment of cryptococcal and coccidioidal meningitis linked to AIDS is fluconazole. Additionally, it is effective in preventing both superficial and potentially fatal fungal infections in immunocompromised people. However, fluconazole prophylaxis should only be administered to HIV-positive individuals or AIDS patients who are refractory and intolerant to topical agents, or to patients with prolonged (+2 weeks) and profound neutropenia (+1500 cells), due to the high cost of this medication and the possibility of resistance developing during therapy. While 100–400 mg qd is the recommended dosage of fluconazole for adults,



greater dosages (+800 mg qd) are needed to treat severe invasive infections and infections caused by *Candida* species with a minimum inhibitory concentration (MIC) of +8. µg/ml.

Nevertheless, inherent resistance to *Candida krusei* and *Candida glabrata* prevents fluconazole from being used to treat infections caused by these yeasts, even when the MIC is attained. Unlike itraconazole and imidazoles, fluconazole does not have significant toxicological side effects (2.8–16%). However, negative side effects are more common when the dosage is raised above 1200 mg. Although they are less common than those seen with ketoconazole and itraconazole, interactions between fluconazole and other concurrent medications are comparable to those described with other azoles. When topical enilconazole is not practical, fluconazole has been used to treat penicilliosis and nasal aspergillosis in small animals and birds.

2.ITRACONAZOLE

:-

Another oral triazole that is sold commercially for the treatment of specific systemic mycoses is itraconazole. Itraconazole, in contrast to fluconazole, is highly protein bound (+90%) and poorly penetrates the CSF and urine but well into the skin and soft tissues. It is also insoluble in aqueous fluids. Although its structure is similar to that of ketoconazole, itraconazole exhibits a wider range of antifungal activity both in vitro and in vivo than both ketoconazole and fluconazole. Itraconazole, like ketoconazole, is better absorbed when the patient is not fasting and is only soluble at low pH. Patients with cancer or those using concurrent H-receptor antagonists, omeprazole, or antacids had inconsistent absorption.

As a result, this medication should be taken with meals and/or acidic liquids. Plasma peak (1.5–4h) and trough concentrations between 1 and 2.2 and 0.4 and 1.8 µg/ml, respectively, are typically obtained following 200-mg dosages (capsule) as either single daily dosages (po or bid) or after IV administration (bid) for two days and qd for additional days. These concentrations are also obtained in cancer patients receiving 5 mg/kg divided into two oral solution dosages. Clinically, itraconazole (200–400 mg/day) has supplanted ketoconazole as first-line treatment for endemic, non-life-threatening mycoses brought on by *Sporothrix schenckii*, *B. dermatitidis*, *C. immitis*, and *H. capsulatum*. Higher dosages are advised for more severe mycoses, and clinical resistance may develop. Additionally, it can be useful as a second-line treatment for infections that are resistant to or intolerant of traditional amphotericin B therapy, such as those caused by *Aspergillus* species and phaeoid (dematiaceous or black moulds or yeasts) fungi. Commercial forms of itraconazole include oral solution, tablets, and intravenous suspension. For the treatment of HIV-associated oral and esophageal candidiasis, particularly in instances that are resistant to fluconazole, the oral solution is more effective than the tablet. However, itraconazole plasma concentrations should be monitored when treating both superficial and invasive diseases: a positive clinical response seems to depend on drug concentrations of +0.5µg/ml by high-performance liquid chromatography and 12µg/ml by bioassay. Compared to ketoconazole, itraconazole treatment has been linked to fewer negative and largely temporary side effects (+110%) These side effects are typically seen when the patient consumes up to 400 mg over multiple periods of time. Although it is rarely used, itraconazole has been used to treat horse sporotrichosis, osteomyelitis brought on by *C. immitis* in large animals, endemic mycoses, aspergillosis, and cryptococcosis in dogs (particularly blastomycosis). Regarding its adverse effects or drug interactions in animals, no information is known. ^[25]

For the treatment of some types of systemic mycosis, triazoles like fluconazole and itraconazole have taken the role of amphotericin B and are now considered the standard for azoles. Fluconazole is now often used to treat candidemia in non-neutropenic hosts and is becoming more widely accepted for usage in the treatment of cryptococcosis and some types of coccidiomycosis. Histoplasmosis, blastomycosis, sporotrichosis, coccidioidomycosis, consolidation treatment for cryptococcosis, and some types of aspergillosis have all been shown to respond well to itraconazole. It is possible to deliver fluconazole intravenously or orally. ^[26]

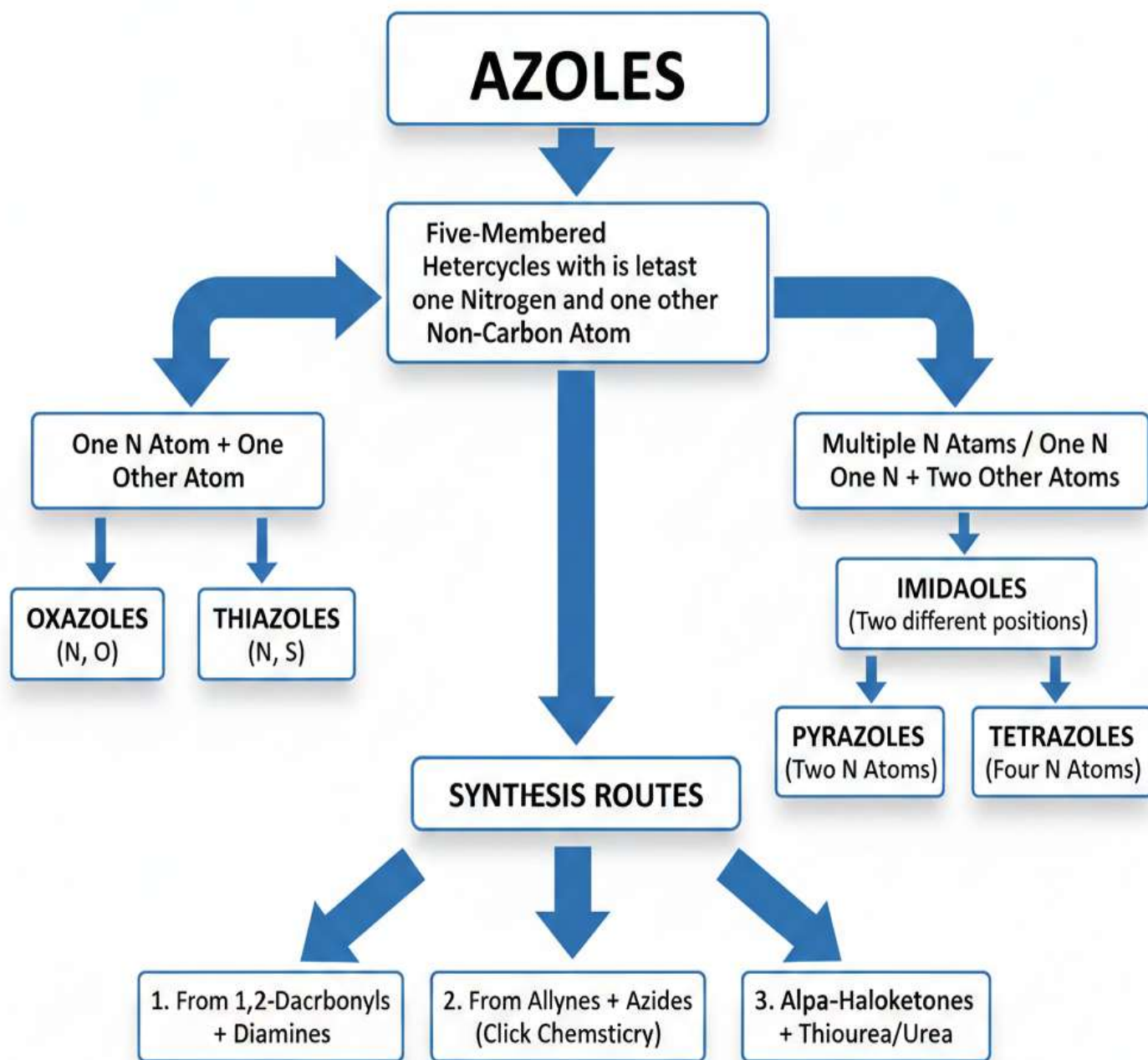


Figure 8: MOA of Azoles



ANTIMETABOLITES AGENT

FLUCYTOSINE

Flucytosine, a pyrimidine analogue, was first created in 1957 as an anti-tumor chemotherapeutic drug. It was soon overshadowed, though, as it turned out to be less effective than other medications. A few years later, in vitro research revealed flucytosine's hitherto undiscovered antibacterial qualities, reigniting interest in the medication in both clinical and experimental settings. Although flucytosine lacks inherent antifungal properties, its metabolite 5-fluorouracil is known to prevent fungal cells from synthesising RNA and DNA. Flucytosine is mostly deaminated by cytosine deaminase in the cytoplasm of fungal cells soon after it is absorbed by cytosine permease.

It should be mentioned that 5-fluorouracil is useless as an antifungal agent since it is extremely toxic to both human and non-human mammalian cells and is not easily absorbed by fungal cells. Currently, its primary application is in the treatment of specific cancers, primarily colorectal carcinoma.

Flucytosine interacts with cytosine permease and cytosine deaminase because it is a fluorinated analogue of cytosine. It shares metabolic routes with cytosine, hypoxanthine, and adenine. Furthermore, uridine monophosphate pyrophosphorylase converts 5-fluorouracil into 5-fluorodeoxyuridine monophosphate, which inhibits thymidylate synthetase (a mechanism of action shared with the chemotherapeutic agent capecitabine) and prevents the synthesis of new DNA molecules. 5-fluorouracil's active metabolite, 5-fluorouridine triphosphate, is incorporated into fungal RNA in place of uridylic acid.

Uridine monophosphate pyrophosphorylase transforms it into 5-fluorodeoxyuridine monophosphate, which inhibits thymidylate synthetase (a mode of action shared with the chemotherapy drug capecitabine) and prevents the creation of new DNA molecules.

The majority of yeasts, such as *Cryptococcus*, *Candida*, and *Torulopsis* species, are susceptible to flucytosine. Flucytosine also affects other kinds of fungi, including *Aspergillus*, *Cladosporium*, *Phialophora*, *Cephalosporium*, *Sporothrix*, and *Blastomyces*. Although they are not well reported, minimal inhibitory concentrations (MIC) have varied greatly, ranging from less than 100 mg/L to more than 1000 mg/L. Significantly, up to 7-8% of strains of several species, including *Candida albicans*, *Candida neoformans*, and *Torulopsis glabrata*, have been found to have inherent resistance; however, these rates vary geographically due to various reasons.

Two primary mechanisms of resistance have been identified: (1) mutations in the enzymes required for the biological processes that flucytosine undergoes, which reduce its final effects; and (2) an upregulation of intrinsic pyrimidine production, which results in a competitive inhibition of flucytosine's metabolites, thereby reducing its antifungal effects.

ALLYLAMINES

TERBINAFINE :-

Terbinafine is effective against almost all clinically significant dermatophyte species at very low concentrations. Terbinafine absorbs easily. It is not required to be taken with meals since, in contrast to itraconazole, its absorption properties do not change when consumed with food. After a single dose, terbinafine achieves its maximum plasma concentrations (0.8 to 1.5 µg/ml) after about two hours. Terbinafine accumulates in the nail plate similarly to itraconazole because it is lipophilic and penetrates keratinising tissue very efficiently. Additionally, the stratum corneum and sebum contain large quantities of terbinafine. Long after the medication has been stopped, terbinafine remains in the nail. Terbinafine concentrations in the nail are significant even after just one month of drug exposure, as Fig. illustrates.

The cytochrome P-450 enzyme system does not break down terbinafine. As a result, there is limited chance of drug-drug interactions, and no clinically significant interactions have been documented.

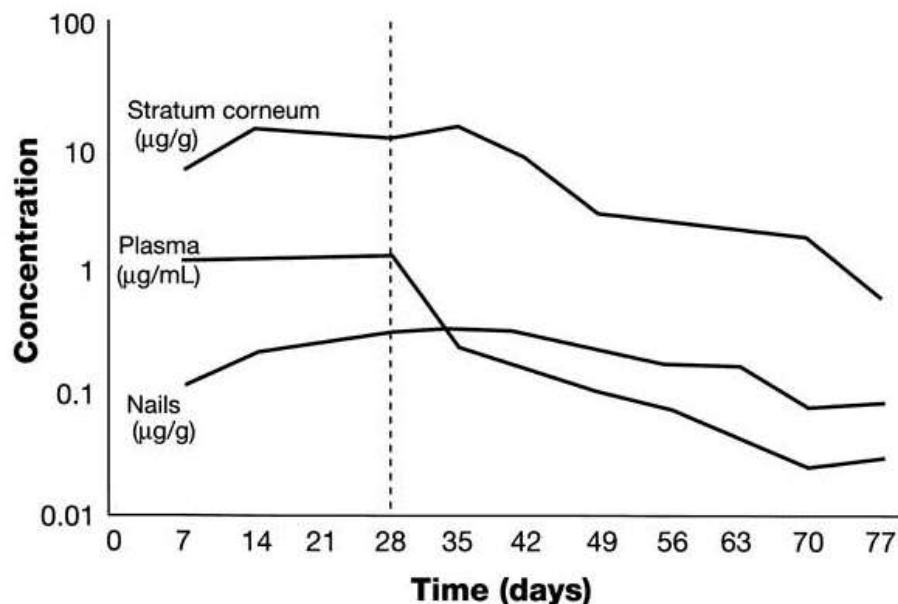


About 20% of terbinafine is eliminated in the faeces, and over 70% is eliminated in the urine. Terbinafine has not been linked to any teratogenic alterations in animals. The FDA has classed it as a Pregnancy Category B agent, which is less stringent than itraconazole's classification.

The following qualities could be on a "wish list" for the "ideal" antifungal agent: Effective against a wide range of fungi at very low concentrations, ideally with fungicidal activity; High cure rate, low relapse rate; good safety profile; no drug interactions; good tissue distribution and keratinophilic and lipophilic properties; brief duration of action.

Compared to many other antifungal medications, terbinafine is more effective at lower concentrations and is very active against a wide variety of fungal species. Instead of having a slower fungistatic effect, it has a main fungicidal activity that kills fungus quickly. Because terbinafine is keratinophilic, it is widely transported to nails and keratinised tissues, where it exhibits lasting activity. Compared to other antifungal treatments, it has significant cure rates and a reduced risk of relapse. Terbinafine has demonstrated a good safety record thus far and has few clinically significant medication interactions.^[27]

Figure 9 : Tissue distribution and persistence of terbinafine after oral





ECHINOCANDINS :-

Due to an increase in invasive fungal infections, candidemia is a significant cause of death in immunocompromised individuals (33 to 47%). Despite being the most prevalent isolate, *C. albicans*-infected patients had the greatest death rate. Additionally, they exhibit a decreased susceptibility to azole antifungals. Due to *C. glabrata*'s growing resistance, fluconazole, which has been the cornerstone of treatment up to this point, is losing ground. One of the main causes of morbidity in patients receiving transplants and those with haematological malignancies is aspergillosis. Nephrotoxicity and infusion-related side effects are extremely common with amphotericin B, which is used to treat invasive fungal infections. The only azole antifungal medication approved for use in invasive aspergillosis is voriconazole. In light of this, the discovery of echinocandins, a novel class of antifungals, represents a promising advancement in antifungal treatment. A class of cyclic, semisynthetic lipopeptides having an N-linked acyl lipid side chain is known as echinocandins. The medications in this class are anidulafungin, micafungin, and caspofungin.

The echinocandins function as non-competitive inhibitors of β - (1, 3)-D-glucan synthase, a crucial part of the fungal cell wall that is absent in humans. Osmotic instability and cell death result from the organism's incapacity to produce β -D-glucan.

When it comes to *Candida albicans*, *Candida parapsilosis*, and *Candida guilliermondii*, echinocandins show strong fungicidal activity. Additionally, there is good action against *Candida glabrata* that is resistant to fluconazole and amphotericin B. While amphotericin B and trizoles have fungicidal effect against *Aspergillus* species, echinocandins have fungistatic activity. Although uncommon, echinocandin resistance has been documented in *C. glabrata* and *C. parapsilosis*.

All echinocandins are exclusively given intravenously due to their low oral bioavailability. The dose does not need to be changed in cases of renal impairment because none of the medications are exclusively eliminated by the kidneys. The dosage of caspofungin must be changed in cases of mild hepatic impairment, although anidulafungin and micafungin do not require this modification.

All three echinocandins have been used in clinical trials for a variety of fungal infections. The first medication in the group to undergo clinical testing was caspofungin. Anidulafungin and micafungin have now been thoroughly investigated.

All of the echinocandins have been associated with infusion-related side effects, including fever, pruritis, rash, oedema, and face flushing. They typically appear right after infusion and react favourably to antihistamines. The pace of infusion should be reduced, but the medication need not be stopped. All three medications have the potential to cause thrombophlebitis. Overall, the infusion-related events seem to be much fewer than those due to amphotericin B. Derangement of hepatic transaminases has been observed in almost all the studies of adverse events of the echinocandins. Liver function should be monitored, especially in case of caspofungin. However, the gross disturbance in creatinine clearance, as observed with amphotericin B, is not seen and these drugs are probably safer than amphotericin B in case of renal impairment. Overall, echinocandins appear to have a tolerability profile that is superior to amphotericin B and similar to fluconazole.

Since echinocandins are strongly protein bound and non-dialyzable, no dose modification is necessary for renal impairment, especially in dialysis patients. Caspofungin dosage adjustments are not necessary for patients with mild hepatic insufficiency, however for those with substantial hepatic insufficiency, a dose reduction to 35 mg is advised. On the first day, a 70 mg loading dose should still be given if the clinical circumstance calls for it. Micafungin and anidulafungin do not require dose adjustment in cases of mild to moderate hepatic impairment. The risk/benefit ratio of continuing micafungin treatment should be assessed for patients who experience abnormal liver function tests while taking the medication. Anidulafungin is not metabolised by the liver, and hepatic impairment of any degree has not been linked to an increase in its serum levels.

None of the three medications have been licensed for use in the paediatric population, despite the fact that echinocandins have been researched in children. For the elderly population, there is no need to modify the dosage. Because all echinocandins have the potential to be toxic to embryos, they should only be taken during pregnancy if the benefits to the mother outweigh the risks to the foetus.



Micafungin may be a more affordable treatment for invasive candidiasis and candidemia than liposomal amphotericin B, according to an economic analysis.^[28]

TOPICAL ANTIFUNGAL AGENTS:-

Topical antifungals are drugs used to treat localised fungal infections that are applied directly to the skin, nails, or mucous membranes. These drugs are particularly effective in treating superficial dermatophytic infections including ringworm (tinea corporis), athlete's foot (tinea pedis), jock itch (tinea cruris), and yeast infections like candidiasis. The capacity of topical antifungals to deliver high concentrations of the active ingredient directly to the site of infection, lowering the risk of systemic toxicity and medication interactions, is their main advantage over systemic antifungals. Topical antifungals function by interfering with different parts of the fungus cell. Depending on the drug's class, the method of action may differ:

Azoles, such as ketoconazole, miconazole, and clotrimazole: Ergosterol, an essential part of the fungal cell membrane, is inhibited by azoles. Fungal cell death results from the membrane becoming excessively porous in the absence of ergosterol, which allows cell contents to flow out.

Allylamines, such as naftifine and terbinafine: Although they operate earlier in the biosynthetic pathway than azoles, allylamines inhibit squalene epoxidase, an enzyme involved in ergosterol production. As a result, harmful sterol intermediates build up and cause cell death.

Polyenes, such as nystatin, bind to ergosterol in the fungal cell membrane to create pores that compromise the integrity of the membrane, allowing internal contents to seep out and causing cell death.

Others (e.g., Ciclopirox, Tolnaftate): Ciclopirox has a broad mechanism that includes interference with DNA, RNA, and protein production as well as disruption of fungal cell membrane transport processes.

It is believed that tolnaftate stunts mycelial growth and distorts the hyphae.

Usage and Indications For a number of superficial fungal diseases, topical antifungals are recommended, such as: Terbinafine, Clotrimazole, or Miconazole are used to treat tinea pedis, often known as athlete's foot. Terbinafine or naftifine are frequently used to treat tinea cruris, sometimes known as "jock itch." Azoles or terbinafine can be used to treat tinea corporis, also known as ringworm. Ketoconazole shampoo or cream is frequently used for tinea versicolor. Creams containing azole or nystatin work well for cutaneous candidiasis. Ketoconazole shampoo works well for treating seborrheic dermatitis. For mild to severe cases of onychomycosis (nail fungus), Ciclopirox nail lacquer is a possibility.

Adverse Reactions and Safety Measures Although topical antifungals are usually well tolerated, some patients may have local adverse effects, including:

Skin Irritation: The application location may experience burning, itching, redness, or stinging sensations.

Get in touch Dermatitis The active ingredient or excipients may cause an allergic response.

Photosensitivity: Certain antifungals, especially azoles, can make you more sensitive to sunshine, which can cause photodermatitis.

Current Developments in Topical Antifungals The treatment of fungal infections has greatly improved with the creation of novel formulations and drug delivery methods:

Formulations of Liposomes and Nanoparticles: These formulations provide larger drug concentrations at the infection site by improving the penetration of antifungal medications into the skin and nails.

Combination Items: It has been demonstrated that combining antifungals with keratolytics (such as urea) or anti-inflammatory drugs increases therapy efficacy, especially in cases that are resistant.

Novel Molecules New drugs with great efficacy and little resistance, such as luliconazole and efinaconazole, are exhibiting encouraging outcomes.^[29]

Tolnaftate: The medication works against *Malassezia furfur* and the majority of dermatophytes, but not *Candida*. The cure rate for tinea pedis is about 80%.^[30]

DISCUSSION :-

Fungal infections represent a growing global health concern, particularly among immunocompromised individuals, patients with diabetes, cancer, HIV/AIDS, and those undergoing organ transplantation. The increasing incidence of both superficial and invasive mycoses, coupled with limited antifungal drug classes and rising resistance, underscores the importance of understanding existing antifungal agents, their mechanisms, advantages, and limitations. This review



critically discusses the major classes of antifungal agents with respect to their pharmacological properties, clinical usefulness, resistance patterns, and safety profiles.

Polyenes, particularly amphotericin B and nystatin, remain among the most potent antifungal agents available. Amphotericin B continues to be regarded as the gold standard for the treatment of life-threatening systemic fungal infections due to its broad spectrum of activity and fungicidal nature. Its ability to bind ergosterol and disrupt fungal cell membrane integrity leads to rapid fungal cell death. However, its clinical utility is significantly limited by dose-dependent nephrotoxicity, infusion-related reactions, and electrolyte disturbances. The development of lipid-based formulations has substantially improved tolerability, reduced renal toxicity, and enhanced patient compliance, although high cost remains a limiting factor. Nystatin, on the other hand, is confined to topical and mucosal use due to systemic toxicity, yet it remains highly effective in superficial candidiasis.

Azole antifungal agents constitute the most widely used class because of their oral availability, relatively favorable safety profile, and broad spectrum of activity. Imidazoles are mainly employed in topical therapy for superficial fungal infections, whereas triazoles such as fluconazole and itraconazole are extensively used for systemic infections. Fluconazole's excellent bioavailability, central nervous system penetration, and predictable pharmacokinetics make it a first-line agent for mucosal candidiasis and cryptococcal meningitis maintenance therapy. However, its limited activity against moulds and increasing resistance among *Candida* species such as *Candida glabrata* and *Candida krusei* restrict its effectiveness. Itraconazole offers broader antifungal coverage, including activity against *Aspergillus* species and endemic mycoses, but its variable absorption, drug–drug interactions, and hepatotoxic potential necessitate careful monitoring. The emergence of azole resistance due to alterations in target enzymes, efflux pump overexpression, and ergosterol pathway mutations remains a significant clinical challenge.

Flucytosine, the only antimetabolite antifungal agent in clinical use, demonstrates valuable synergistic activity when combined with amphotericin B, particularly in cryptococcal meningitis. Its ability to inhibit fungal DNA and RNA synthesis provides a unique mechanism distinct from membrane-targeting drugs. Nevertheless, rapid development of resistance during monotherapy and potential hematological and gastrointestinal toxicity limit its standalone use. Therefore, flucytosine is primarily employed as part of combination therapy to enhance efficacy and reduce resistance development.

Allylamines, represented chiefly by terbinafine, play a crucial role in the management of dermatophytic infections. Terbinafine's fungicidal activity, high affinity for keratinized tissues, prolonged persistence in nails and skin, and minimal drug interactions make it the drug of choice for onychomycosis and chronic dermatophytosis. Compared to azoles, terbinafine demonstrates superior cure rates, shorter treatment duration, and lower relapse risk. Its favorable safety profile further supports its widespread clinical use, particularly in long-term therapy.

Echinocandins represent a major advancement in antifungal therapy, particularly for invasive candidiasis and refractory infections. By inhibiting β -(1,3)-D-glucan synthesis, echinocandins target the fungal cell wall—a structure absent in human cells—thereby offering selective toxicity and excellent tolerability. Caspofungin, micafungin, and anidulafungin have shown strong efficacy against azole-resistant *Candida* species and acceptable activity against *Aspergillus*. Their low nephrotoxicity and minimal drug interactions make them preferable in critically ill patients. However, limitations such as intravenous-only administration, high cost, and emerging resistance in some *Candida* species restrict their broader use.

Topical antifungal agents remain the mainstay of therapy for superficial fungal infections. Azoles, allylamines, polyenes, and agents such as ciclopirox and tolnaftate effectively treat dermatophytosis, cutaneous candidiasis, and pityriasis versicolor. The advantages of topical therapy include localized drug delivery, minimal systemic absorption, reduced adverse effects, and good patient compliance. Recent advances in formulations, including nanoparticle and liposomal systems, have further enhanced drug penetration and therapeutic outcomes. However, poor adherence and premature discontinuation remain common causes of treatment failure and recurrence. Overall, the discussion highlights that while current antifungal agents are effective, each class has inherent limitations related to toxicity, resistance, spectrum of activity, and cost. The restricted number of fungal-specific drug targets further complicates antifungal drug development.



Therefore, rational drug selection based on infection severity, fungal species, patient factors, and resistance patterns is essential. Continued research into novel antifungal targets, improved drug delivery systems, combination therapies, and immunomodulatory approaches is critical to overcome existing challenges and improve clinical outcomes in fungal infections.

CONCLUSION:-

Fungal infections continue to pose a significant and growing challenge to global healthcare due to their increasing prevalence, high morbidity and mortality in immunocompromised patients, limited therapeutic options, and the emergence of drug-resistant fungal strains. This review highlights the importance of antifungal agents in the effective management of both superficial and invasive fungal infections and provides a comprehensive overview of their classification, mechanisms of action, clinical applications, and limitations.

The currently available antifungal drug classes—including polyenes, azoles, antimetabolites, allylamines, echinocandins, and topical antifungal agents—play a crucial role in fungal disease management. Polyenes, particularly amphotericin B, remain highly effective for severe systemic infections despite their associated toxicity. Azoles continue to be widely used because of their broad spectrum and oral availability, although resistance and drug interactions remain important concerns. Antimetabolites such as flucytosine are valuable in combination therapy, while allylamines like terbinafine offer highly effective and safer treatment options for dermatophytic infections. Echinocandins represent a major advancement in antifungal therapy due to their selective mechanism of action and improved safety profile, especially in critically ill patients.

Despite these advancements, antifungal therapy is still limited by a narrow range of drug targets, toxicity issues, diagnostic delays, and increasing antifungal resistance. The similarities between fungal and human cells further restrict the development of selective antifungal drugs. Therefore, careful drug selection, appropriate dosing, combination therapy, and monitoring for adverse effects are essential for successful treatment outcomes.

In conclusion, although existing antifungal agents have significantly improved the management of fungal infections, there remains an urgent need for the development of novel antifungal drugs with improved efficacy, reduced toxicity, broader spectrum of activity, and lower resistance potential. Future research focusing on new molecular targets, advanced drug delivery systems, immunotherapeutic strategies, and rapid diagnostic techniques will be essential to enhance antifungal treatment and reduce the global burden of fungal diseases.

REFERENCES :-

1. McGinnis MR, Tying SK. Introduction to Mycology. In: Baron S, editor. *Medical Microbiology*. 4th ed. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Bookshelf ID: NBK8125.
2. Ainsworth G. Fungus Infections (Mycoses). In: Kiple KF, editor. *The Cambridge World History of Human Disease*. Cambridge: Cambridge University Press; 1993. p. 730–736. DOI:10.1017/CHOL9780521332866.117.
3. Santana AE, Sellera FP. Etymologia: Dermatophyte. *Emerg Infect Dis*. 2020;26(9):2156
4. Homei A, Worboys M. *Fungal disease in Britain and the United States 1850–2000: Mycoses and modernity*. Basingstoke (UK): Palgrave Macmillan; 2013.
5. Krishna S, Ahmad S, Zarea M, et al. Title of the article. *Frontiers in Microbiology*. 2021;12:652725. doi:10.3389/fmicb.2021.652725.
6. White T, Henn M, et al. *Trichophyton rubrum*. MicrobeWiki [Internet]. Kenyon College;
7. Fang W, Latgé J-P. Microbe Profile: *Aspergillus fumigatus*: a saprotrophic and opportunistic fungal pathogen. *Microbiology*. 2018;164:1009–1011.
8. Zaragoza O. Basic principles of the virulence of *Cryptococcus*. *Virulence*. 2019;10(1):490–501.



9. Buchanan KL, Murphy JW. What Makes *Cryptococcus neoformans* a Pathogen? *Emerging Infectious Diseases*. 1998;4(1):71–83.
10. Forsberg K, Woodworth K, Walters M, Berkow EL, Jackson B, Chiller T, Vallabhaneni S. *Candida auris: The recent emergence of a multidrug-resistant fungal pathogen*. *Medical Mycology*. 2019;57(1):1–12. doi:10.1093/mmy/myy054
11. Chander J. *Textbook of Medical Mycology*. 4th ed. New Delhi: Jaypee Brothers Medical Publishers; 2017.
12. Bouz G, Doležal M. *Advances in Antifungal Drug Development: An Up-To-Date Mini Review*. Pharmaceuticals (Basel). 2021 Dec 16; 14(12):1312. DOI: 10.3390/ph14121312. PMID: 34959712.
13. Georgopapadakou NH, Walsh TJ. Antifungal agents: chemotherapeutic targets and immunologic strategies. *Antimicrob Agents Chemother*. 1996;40(2):279-291.
14. Perfect JR. The antifungal pipeline: a reality check. *Nat Rev Drug Discov*. 2017;16(9):603-16.
15. Arvanitis M, Mylonakis E. Diagnosis of invasive fungal infections: current limitations and emerging techniques. *Ann N Y Acad Sci*. 2015;1354(1):1-11.
16. Primer – The Fungi. Stajich Laboratory, et al. *Primer – The Fungi*. Public Library of Science. 2009;7(9):e1000550. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC2913116/>
17. Cole GT. Basic Biology of Fungi. In: Baron S, editor. *Medical Microbiology*. 4th ed. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 73. Available from:
18. de Groot PWJ, Bader O, de Boer AD, Weig M, Chauhan N. Adhesins in human fungal pathogens: Glue with plenty of stick. *Eukaryot Cell*. 2013 Apr;12(4):470–481. doi: 10.1128/EC.00364-12
19. Bowman SM, Free SJ. The structure and synthesis of the fungal cell wall. *Bioessays*. 2006 Aug;28(8):799-808.
20. Lenardon MD, Munro CA, Gow NAR. Chitin synthesis and fungal cell wall architecture. *Microbiology*. 2010 Nov;156(Pt 11):3632-44.
21. Chander J. Textbook of Medical Mycology: Antifungal Agents (Review Article). *Int J Med Rev*. 2018;5(2):54-64.
22. Schaechter M, editor. *Desk Encyclopedia of Microbiology*. Elsevier; 2003. ISBN: 008047246X. p. 47.
23. Carolus H, Pierson S, Lagrou K, Van Dijck P. Amphotericin B and other polyenes — discovery, clinical use, mode of action and drug resistance. *J Fungi* (Basel). 2020;6(4):321. doi:10.3390/jof6040321.
24. Schaechter M, editor. *Desk Encyclopedia of Microbiology*. Elsevier; 2003. ISBN: 008047246X. p. 47.
25. Carolus H, Pierson S, Lagrou K, Van Dijck P. Amphotericin B and other polyenes — discovery, clinical use, mode of action and drug resistance. *J Fungi* (Basel). 2020;6(4):321. doi:10.3390/jof6040321.
26. Baracaldo-Santamaría D, Cala-García JD, Medina-Rincón GJ, Rojas-Rodríguez LC, Calderon-Ospina CA. Therapeutic Drug Monitoring of Antifungal Agents in Critically Ill Patients: Is There a Need for Dose Optimisation? *Antibiotics* (Basel). 2022;11(5):645. doi:10.3390/antibiotics11050645.
27. Leyden JJ, McGinley KJ, Smith TF, Grove GL. Pharmacokinetics and pharmacology of terbinafine and related antifungal agents. *Journal of the American Academy of Dermatology*. 1998;38(1):S1-S8. doi:10.1016/S0190-9622(98)70483-9.
28. Grover ND. Echinocandins: a ray of hope in antifungal drug therapy. *Indian J Pharmacol*. 2010;42(1):9– 11. PMID:20606829; PMCID:PMC2885632.
29. Topical antifungals: comprehensive guide for doctors and healthcare professionals [Internet]. Forum for Medical Professionals; c2019
30. IFTM University. Antifungal agents [Internet]. Moradabad (India): IFTM University; 2018