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A REVIEW ON ANTIFUNGAL SYNTHETIC DRUGS AND HERBAL PLANT

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ABSTRACT

Fungi can infect the skin, nails, hair, mucous membranes, and bloodstream. This condition is known as mycosis. These days, the majority of fungal infections, like candidiasis, can vary from a superficial infection of the mucous membrane to potentially fatal systemic mycoses. More than 3 million people die from fungal infections each year. This high figure illustrates how difficult it is to treat these illnesses globally. The effective treatment of fungal diseases has been greatly aided by the recent development of novel antimycotic agent. Antifungal drug such as(Ketoconazole, Fluconazole, and Itraconazole), fluoropyrimidine (Flu cytosine), and polyene antibiotics (Amphotericin B).Antifungals destroy or stop the growth of In order to effectively and completely cure a variety of fungal infections, Ayurveda offers a combination of internal and external medications and therapies. In addition to causing a variety of symptoms and illnesses, fungi can impact different body parts. Ayurveda recommends a different course of action for every kind of infection. To treat fungal infections, antifungal drugs are used. They can stop fungi from growing or directly kill them. Ayurveda uses a lot of unrefined medications to treat fungus infections and other illnesses. Certain medicinal plants, like guava, garlic ginger, neem, and holy basil, are used to treat fungal infections.

KEYWORD: Mycosis or Fungal infection, Antifungal agent, candidiasis, Ayurveda, Medicinal plant.

INTRODUCTION

Pharmaceutical fungicides or fungistatic known as antifungal medication. An antifungal medication that reduces host toxicity while specifically removing fungal infections.[1] Most cases of bloodstream infections caused by Candida spp. are linked to surgery, haematological malignancies, solid tumors, or intensive care units.[2]

Pathophysiology of fungal infection

Most fungi don't harm healthy people, but in those with weak immunity or damaged tissues, they can invade and cause disease. Therefore, serious fungal infections are usually opportunistic infections.[3,4] Genetic differences in immune response may affect susceptibility to fungal infections, but the main risk factor remains severe immune system damage. Patients receiving treatment for blood cancers often lose natural defences, making them highly prone to invasive fungal infections.

Factors that encourage invasion

- Granulocytopenia
- Reduced immunity of cells
  -viruses, such as cytomegalovirus Corticosteroids, cyclosporine
  -purine antagonists, cytotoxic medications (cyclophosphamide),
- Damage to the mucosal barrier
- Unsanitary conditions
- Genetic susceptibility
- Utilizing antimicrobials and adjusting a patient's microbiological environment
- Patients who have co-morbidity are getting older.
- H2 receptor antagonist usage
- Central venous lines
- Current surgery on the gastrointestinal tract

The majority of mycosis is caused by ingestion or inhalation of the environment. Candida, normally present in the mouth and gut. A immunosuppressed person, especially those on chemotherapy, it can enter the bloodstream (candidemia). Antibiotics disrupt normal flora, causing Candida overgrowth, and the gut is now seen as a major source of systemic Candida infections.[5,6]

A) Synthetic Drug as a Antifungal Agent

1. Amphotericin

Amphotericin B is an antifungal medication used to prevent mycosis.[7] It is typically given intravenously[8] It is combined with flucytosine to treat certain infections.[9]

MOA

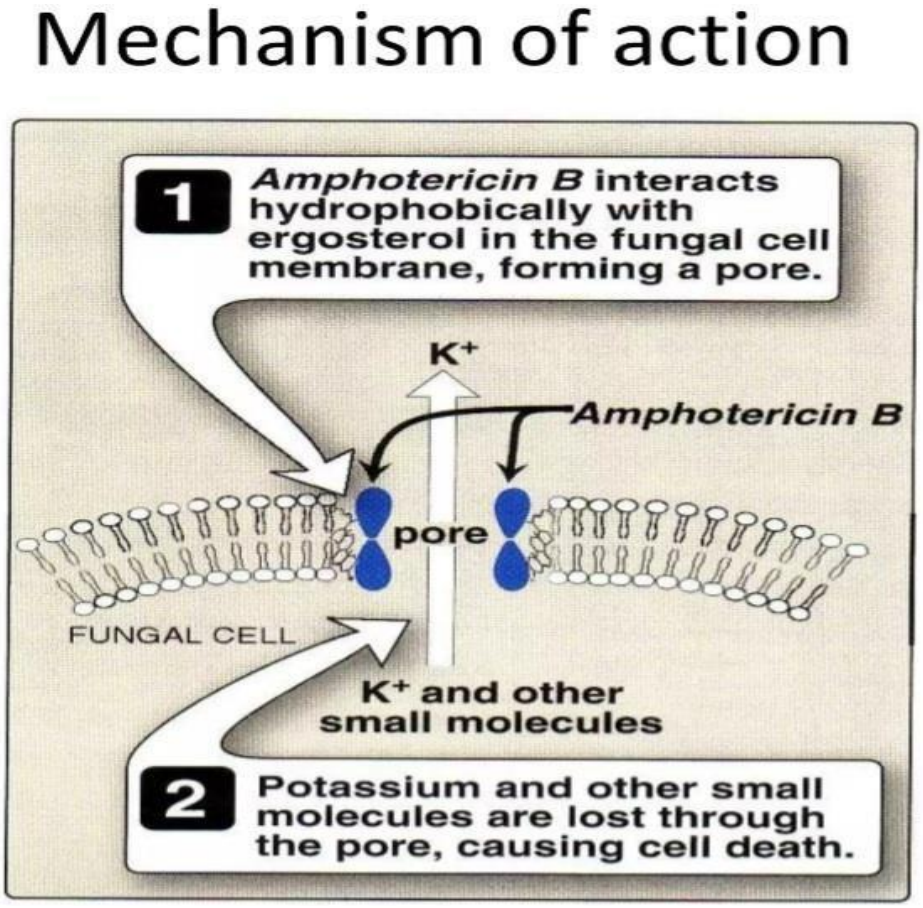

Fig 1: Mechanism of Amphotericin B.

Amphotericin B

↓

Ergosterol in fungal cell membrane

↓

Forms pores in cell membrane

↓

Cell contents leak out

↓

Cell death

Side Effect

- Electrolyte imbalance
- Cardiovascular issue
- Liver function changes
- Anemia[10,11]

Uses

1. The recommended drug for potentially lethal systemic mycoses such as cryptococcal meningitis and histoplasmosis
2. Specifically, mucormycosis associated with diabetic ketoacidosis and post-COVID mucormycosis are treated with liposomal amphotericin B.[12]

2. Ketoconazole

It comes in oral and topical forms. Because of hepatotoxicity, oral use is now restricted.[13] When applied topically, it treats fungal skin infections like cutaneous candidiasis, and dandruff.[14]

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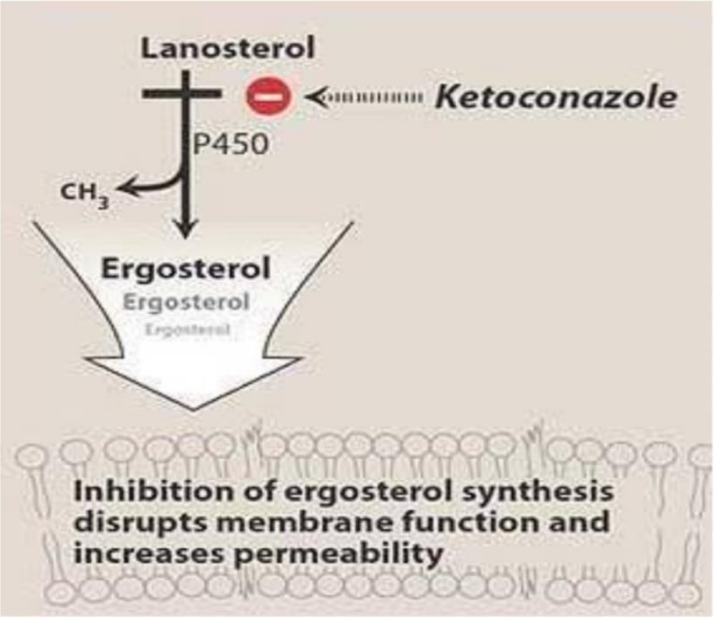

Fig. 2: Mechanism of Ketoconazole.

Side Effect

- gynecomastia
- loss of hair

- menstrual irregularities
- urticaria.
- abdominal pain,
- dry mouth,
- Hepatotoxicity[15]

Uses

1. Topical applications of ketoconazole include ringworm, athlete's foot, and candidiasis.[16]
2. Another systemic medication, ketoconazole, is authorized to treat prostate cancer, chromomycosis, Cushing syndrome and blastomycosis.[17,18]

3. Fluconazole

It can be administered intravenously or orally.[19] The indications include treating oropharyngeal, esophageal infection . Fluconazole can also be used to treat HIV infection.[20]

MOA

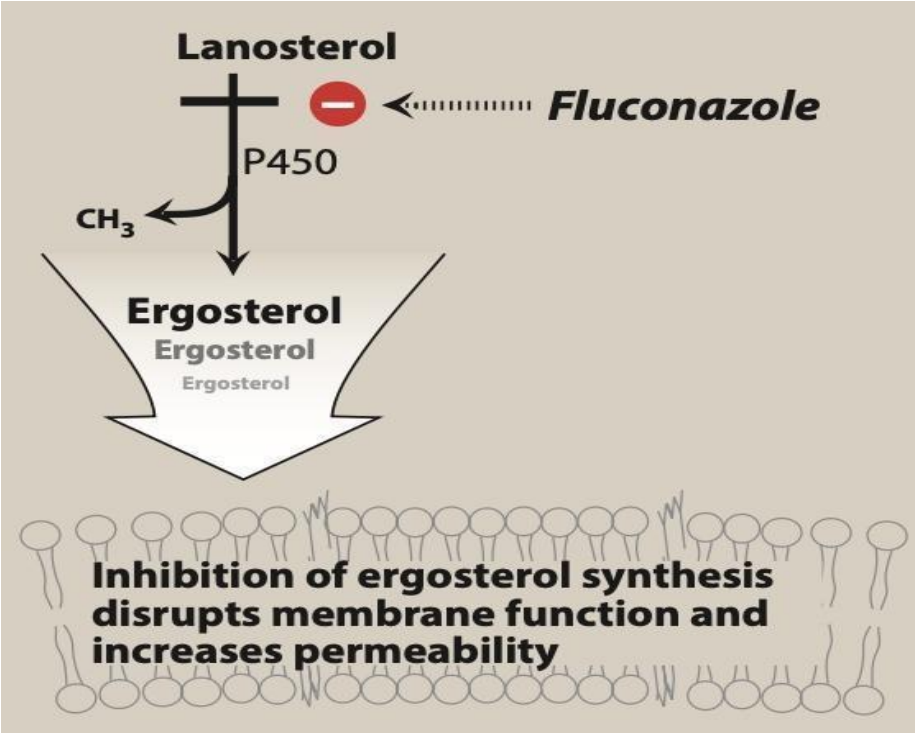

Fig 3: Mechanism of Fluconazole

Side Effect

- Mild headaches
- Dizziness[21]

- anorexia
- abdominal pain
- Hepatotoxicity

Uses

1. fluconazole is used to treat candidal infections and cryptococcosis in the US.[22]
2. Fluconazole as a second-line medication to treat a central nervous system fungal infection.
3. Preventing Candida infections in individuals with compromised immune systems, including those who have advanced HIV infections and premature babies.[23]

4. Econazole

Econazole used as antifungal agent. Fungal cytochrome P450 enzyme lanosterol 14-α-demethylase is being inhibited. Stops the production of ergosterol in the fungal cell membrane.[24]

MOA

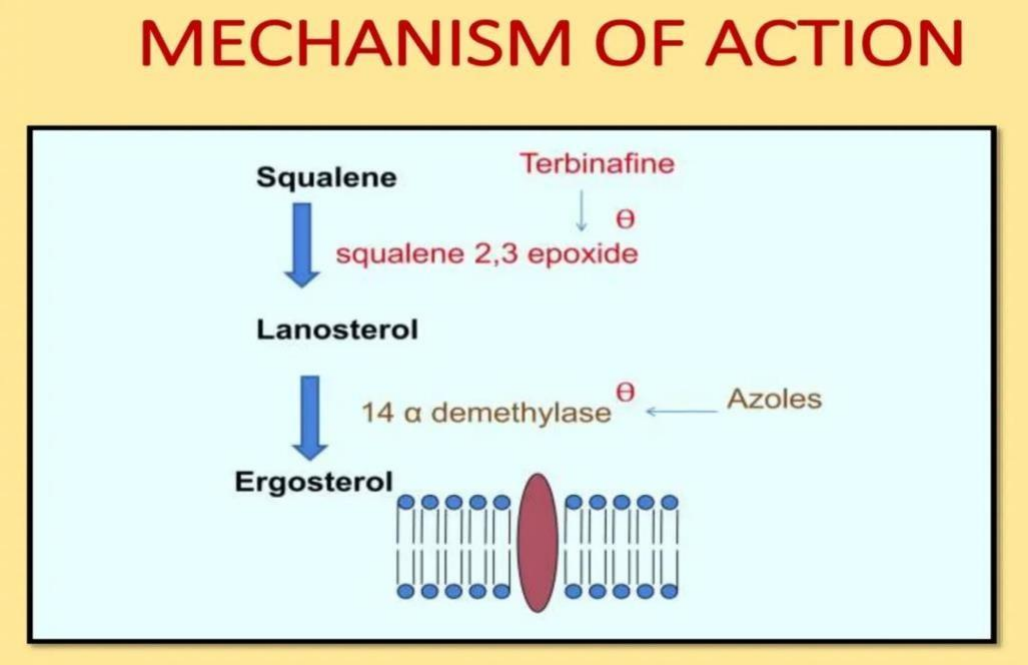

Fig 4: Mechanism of Econazole.

Lanosterol 14-α-demethylase, is inhibited by antifungal substances in a non-competitive manner. The fungal cell membrane becomes unstable as a result of this action, which causes cell lysis, cell death, and content leakage.[25]

Side Effect

- burning,
- Itching,
- redness (erythema)[26]
- Hepatotoxicity

Uses

1. Econazole is applied topically to treat skin infections like jock itch, ringworm, pityriasis versicolor, athlete's foot, and tinea.[27]
2. It is well known that econazole binds to tubulin and prevents it from polymerizing.[28]

5. Terbinafine

Terbinafine is a synthetic allylamine antifungal that is applied topically and taken orally. One of the most widely used medications for onychomycosis and tinea infections, it is very effective against dermatophytes. It is sold under a number of brand names, such as Lamisil.[29] It is applied topically as an ointment or cream, or it can be taken orally.[30]

MOA

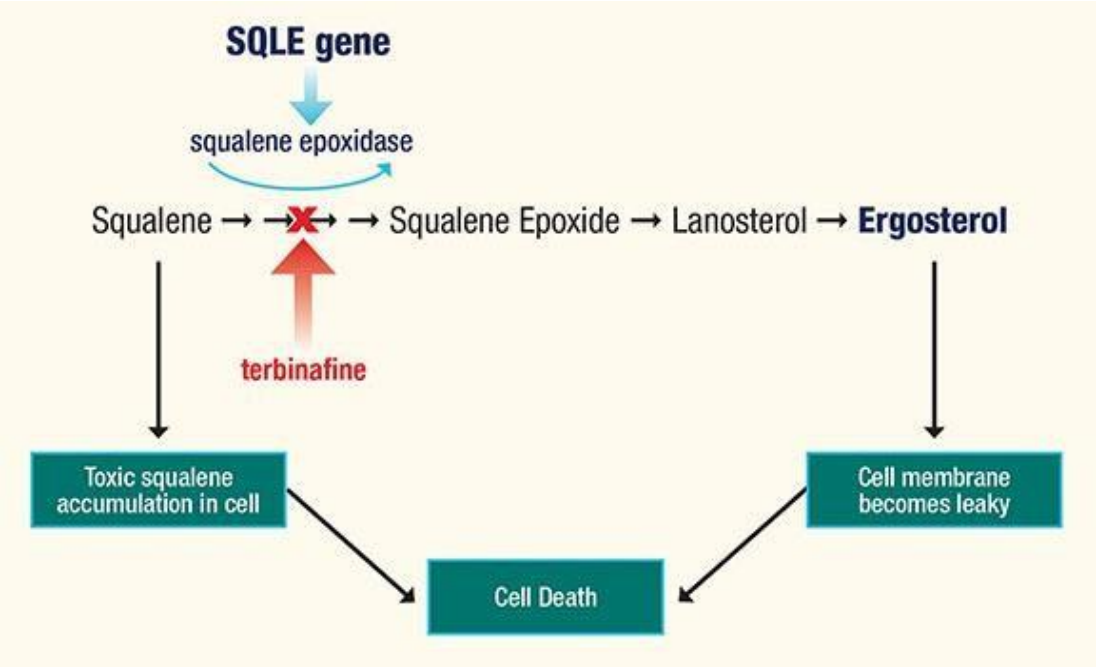

Fig. 5: Mechanism of Terbinafine.

Terbinafine is one example of an allylamine that inhibits the rate-limiting enzyme squalene epoxidase, which is in charge of producing the precursors to ergosterol. The loss of cell membrane integrity is the mechanism of action of this kind of medication.[31]

Side Effect

- nausea, diarrhoea,
- headache, anxiety
- cough, Depression
- liver problem
- Allergic Reaction[32]

Use

1. It also effective for scalp fungal infection
2. Terbinafine is approved for both topical and systemic (oral) use[33]

Table 1: Classification of Antifungal agent.

Class of Drug	MOA of Drug	Example
Allylamine	Allylamine inhibits the squalene epoxidase enzyme, which prevents the synthesis of ergosterol	Terbinafine
Antimetabolite	The antimetabolite stops fungal DNA synthesis by using 5-fluorodeoxy-uridine monophosphate to block thymidylate synthetase, and it stops fungal protein synthesis by substituting 5 fluorouracil for uracil in fungal RNA	Flucytosine
Azole	Inhibition of the 14a- demethylase enzyme of cytochrome P450. This enzyme is part of the pathway for sterol biosynthesis, which converts lanosterol to ergosterol.	Fluconazole Ketoconazole
Polyene	When this binding occurs, the membrane depolarizes and pores form, increasing permeability to monovalent and divalent cations as well as proteins and ultimately leading to cell death.	Amphotericin B

B) Herbal Plant as a Antifungal Agent

1. Neem

Fig 6: Neem.

One important active ingredient in neem, azadirachtin, has evidence.[34] Fungal cell membranes contain ergosterol, a sterol that is essential for preserving the fluidity and integrity of the membrane.[35] Organoleptic character: The leaves are 20–37 cm long and lanceolate with a serrated shape.

- Pseudonym: Holy tree
- Natural Source : Neem consist fresh or dried leaves of melia azedarach. L, which belongs to the Meliaceae family.
- Chemical constituent: Neem's active ingredients include nimbosterol, mellacin

Uses

1. Nimbin, nimbidine, and neem oil are effective against fungus.
2. Additionally, it has insecticidal and antiseptic properties.
3. It treats AIDS and has antiviral and antifertility qualities.

2. Holy Basil

Fig 7: Holy Basil.

It is reddish-black in color, and the flowers are purplish. Hinduism places a high value on its antimicrobial and antioxidant qualities, which may help lower blood sugar and cholesterol, protect against toxins, and reduce stress. The leaves are typically drunk as tea or juice, which is added to food, and the roots and seeds are used for a number of therapeutic uses.

- pseudonym: Krishna Tulsi
- Natural Source: It is obtained leaves of Ocimum tenuiflorum of family Lamiaceae
- Chemical constituent : 20% eugenol methyl ether, 3% carvacrol, and 70% eugenol are also present. Additional components include caryophylline, fixed oil, tannin, saponin, and traces of alkaloids.

Uses:

1. The antifungal activity of Ocimum Sanctum leaves against clinically isolated dermatophytes was 200 µg/mL.
2. Insecticidal, antiviral, antitussive, and antibacterial properties are also employed.[36]

3. Garlic

Fig. 8: Garlic.

For centuries, traditional medicine has used garlic, which has a strong aroma and a unique flavour, for a number of health reasons. Allicin, the main bioactive ingredient in garlic that gives it its strong antifungal action against filamentous fungi and yeast, is one of the many organosulfur compounds that give it its therapeutic qualities.[37] By interfering with the synthesis of ergosterol, allicin modifies the structure and function of the fungal membrane, ultimately compromising the integrity of the cell membrane and leading to cell death.[38]

- Synonyms: Allium sativum
- Biological source : Garlic is the ripe bulb of the plant Allium sativum, belonging to the family liliaceae
- Chemical Constituent :It has 6.36% protein, 0.5% fat, 33.06% Uses :

1. Garlic’s ajoene compound has anti-tumoral, anti-fungal, antithrombotic, and antiparasitic properties.
2. Ajoene’s recently discovered antifungal property is the subject of this study, along with its possible applications in the treatment of various fungal infections.[39]

4. Ginger

Fig. 9: Ginger.

For more than 200 years, Traditional Chinese Medicine has utilized ginger (Zingiber officinale) as a spice and medicine. The results obtained point to the potential of ginger extract as a food and pharmaceutical industry additive.[40] There are several components in ginger that have antifungal and therapeutic properties.[41]

- Pseudonyms: Shunti
- Chemical constituent :It contains 1 to 2% volatile oil, zingiberene

Uses

1. Traditionally, ringworm patches are treated with ginger paste or decoction.
2. Ginger is a naturally occurring antifungal agent that works against a variety of harmful fungi and is beneficial for food preservation, oral infections and skin infections.[42]

5. Guava

Fig. 10: Guava.

- Pseudonym: yellow guava, or lemon guava.
- Natural Source: guava is the tropical plant Psidium pomiferum.
- Chemical constituent: The leaves are rich in rutin, naringenin, epicathechin, gallic acid, isoflavonoids. Carotenoids and ascorbic acid are abundant in the pulp. Quercetin is present in the fruit.

Uses

1. Secondary metabolites in Psidium guajava have demonstrated antifungal activity. The fractions prevented Candida spp. from growing as fungi.
2. Inflammation, diabetes, high blood pressure, dental cavities, wounds, pain, fever, diarrhoea, rheumatism, lung conditions, and ulcers are among its uses.[43]

CONCLUSION

A major global health concern, fungal infections, also referred to as mycoses, have a high rate of morbidity and mortality. In order to treat these infections, antifungal medications are essential because they either prevent fungal growth or eradicate the infection. Amphotericin B, ketoconazole, fluconazole, econazole, and terbinafine are examples of synthetic antifungal drugs that are very helpful in treating superficial and systemic mycoses because they target ergosterol synthesis or cell membrane integrity. On the other hand, continuous use of them can lead to adverse effects and resistance issues. Herbal remedies are now a good alternative because of their accessibility, safety, and abundance of bioactive ingredients. Important antifungal activity is exhibited by medicinal plants such as guava (Psidium guajava), ginger (Zingiber officinale), garlic (Allium sativum), holy basil (Ocimum sanctum), and neem (Azadirachta indica) through mechanisms such as inhibition of ergosterol synthesis, disruption of cell membranes, and interference with fungal enzyme systems.

An efficient, all-encompassing method of treating fungal infections can be achieved by combining the advantages of contemporary antifungal treatment with Ayurvedic herbal remedies. The development of safer, more effective antifungal agents with fewer side effects and a lower potential for resistance may result from further research into the bioactive ingredients and mechanisms of medicinal plants.

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