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Terbinafine; an Antimycotic Agent.

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ABSTRACT-One of the most commonly transmitted illnesses is fungus, generally known as mycosis. Terbinafine, a synthetic allylamine antifungal agent, is one of the antifungal medicines available and used to treat fungal infections. The numerous types of fungal infections, their symptoms, and treatment are discussed in this review, along with the efficient use of terbinafine for fungal infection, as well as their pharmacokinetics, pharmacodynamics, mechanism of action, history, and dose for various infections. Athlete's foot, Joch itch, ringworm, yeast infection, and onychomycosis are examples of infections that can affect many regions of the body, such as the nail, foot, hand, and so-on.

Key words-Terbinafine, mycotic, dermatophyte, onchomycosis.

INTRODUCTION-

Anyone can have a fungus infection, and it can arise on any region of the body. A woman with a vaginal yeast infection, a jock with athlete's foot, and a baby with thrush are just a few examples. Fungi are microorganisms that have a material called chitin in their cell walls. Many varieties of mushrooms, as well as some fungi, are edible. Other fungus, such as aspergillus, is exceedingly poisonous and can cause life-threatening illnesses. Fungal infections can be caused by a variety of fungi. Fungi that aren't normally found on or inside your body can colonise it and cause an illness in some situations. Fungi that are typically present on or inside your body can multiply out of control in other instances, resulting in an infection. Infections caused by fungi are infectious. They can the ability to spread from one person to another. In rare circumstances, disease-causing fungi can be transmitted from infected animals or polluted soil or surfaces [1].Dermatophytosis is a fungal infection caused by dermatophytes, a fungus that invades dead keratin in order to gather nutrients. Dermatophytosis is still one of the most common skin disorders worldwide, with varying levels of incidence in various nations. Dermatophytes are fungi that are anthropophilic (human), zoophilic (animal), and geophilic (including human and animal) (soil). Trichophyton (skin, nail, and hair infection), Epidermophyton (grows on the outer layer of the skin and causes tinea infection), and Microsporum (grows on the outer layer of the skin and causes tinea infection) are the three genera of Dermatophytosis (causes ringworm)[2].The deleterious effects of these fungi on human health are becoming more severe, and fungal diseases now have larger global death rates than malaria or breast cancer [2]. To treat fungal infections, a variety of methods have been developed, including topical creams, oral antifungal medicines, suppository, and even surgery [3],[5]. In humans, antifungal medicines such azoles are the most prevalent and commonly utilized first line of defense [6]. Antifungal drugs, on the other hand, can only control fungal diseases for a short period of time due to fungi's extremely flexible genomes and ability to multiply quickly, allowing them to evolve variants and develop resistance to the chemicals. Hepatotoxicity, gastrointestinal dysfunction, drug eruption, and allergy are all possible adverse effects of antifungal medications [7–9].Further, while most antifungal drugs are lipophilic, their high molecular mass causes poor penetration and, as a result, low concentration in cutaneous tissues, resulting in infection recurrence and recurrent therapy [10], [11]. As a result, there is still a need for an effective antifungal medicine that can prevent resistance, decrease side effects, and increase penetration [12]. Itraconazole, ketoconazole, terbinafine hydrochloride, and other oral medications are currently used to treat onychomycosis, and they must be taken for at least three months to be effective [13].

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There are just a few novel treatments for dermatophyte infection. Even when new, most antifungal medications belong to one of two pharmacological families: azoles or allylamines; a novel family, echinocandins, is primarily exclusively utilized for systemic Candida/Aspergillus infection [14-15]. Marketing of broad-spectrum topical agents, use of topical agents with anti-inflammatory as well as antifungal properties, and use of a combination of existing oral antifungal agents, or oral/topical antifungal agents, have all been used to improve monotherapy cure rates in the treatment of dermatophytes [16].Terbinafine is an allylamine antifungal medication that was originally licensed for the treatment of onychomycosis in the United Kingdom and the United States in the 1990s. It has been claimed to be superior to griseofulvin, itraconazole (ITZ), and fluconazole (FLZ) in the treatment of dermatophytoses and toenail onychomycosis in a number of randomized, controlled trials [17-18]. It has good in vitro action against Trichophytonrubrum, Trichophytonmentagrophytes, and Epidermophytonfloccosumdermatophytes, as well as ringworm diseases such Tineapedis, Tineacruris, Tineacorporis, and Tinea inguinal [16], [19].For the treatment of most dermatomycoses and ringworm infections, it has replaced griseofulvin. TRB has been shown to be effective in vitro and in vivo against a variety of new nondermatophytic fungal infections, including yeast (Candida and Cryptococcus spp.), dematiaceous and filamentous moulds, and azole-resistant isolates, since its debut in the 1990s. Despite its strong in vitro activity, terbinafine therapeutic usefulness in the therapy of these infections is unknown at this time [20].

Drug details-

BCS Class	Class II (low solubility, high permeability)
Chemical Formula	$C_{21}H_{25}N.HCL$
Molecular Weight	327.9 Dalton
IUPAC Name	(2E)-6,6-dimethylhept-2-en-4-yn-1-yl](methyl)(naphthalen-1-ylmethyl)amine hydrochloride.
Appearance	White to off-white solid
Melting Point	204-208°C
Log p value	5.51
pKa value	8.94
Half life	16.4 to 26.1 hrs.
Solubility	Freely soluble in methanol and dichloromethane, Soluble in ethanol.

Table A; Drug details [32]

History of Terbinafine –

Terbinafine is a synthetic allylamine that was created in 1979 by modifying naftifine chemically, with the results of the synthesis published in 1984. Naftifine was discovered by chance and showed antifungal efficacy, however it

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was only appropriate for topical usage. However, terbinafine, an orally and topically active antimycotic with significant in vitro activity against a wide range of fungi, was developed after an intensive derivatization programme (>1000 analogues) based on this prototype [21].

Terbinafine was originally made available in Europe in 1991, and then in the US in 1996. The first generic versions of prescription Lamisil (terbinafine hydrochloride) pills have been approved by the US Food and Drug Administration. Lamisil's remaining patent or exclusivity period ended on June 30, 2007. The FDA announced on September 28, 2007, that terbinafine is a novel therapy for children aged four and up. To cure tineacapitis (scalp ringworm), antifungal granules can be put on a child's meal [22].

Types of fungal infection, symptoms and treatment-

A fungal infection is also known as mycosis. Although most fungi are harmless to humans, some of them are capable of causing diseases under specific conditions. Fungi reproduce by releasing spores that can be picked up by direct contact or even inhaled. That's why fungal infections are most likely to affect skin, nails, or lungs. Fungi can also penetrate the skin, affect organs, and cause a body-wide systemic infection.

Some common types of fungal infection include:

a) Athlete's foot (Tinea pedis)
b) Jock itch
c) Ringworm
d) Yeast infection
e) Onychomycosis or a fungal infection of the nail.

Some types of fungi don't normally cause infections in humans but can cause sickness in people with weakened immune systems. These are called opportunistic infections. [1] , [33].

a) Athlete's foot-

Tinea pedis, popularly known as athlete's foot, is an infectious fungus that infects the skin on the feet. It can also affect the hands and toenails. Because it is so frequent in athletes, the fungal infection is known as athlete's foot. An athlete's foot isn't a serious condition, but it can be difficult to treat.

When the tinea fungus spreads on the feet, it is known as athlete's foot. The fungus can be contracted by direct contact with an infected person or by touching fungus-infested surfaces. Warm, damp surroundings are ideal for the fungus to thrive. Showers, locker room floors, and swimming pools are all frequent places to find it.

Symptoms-

- ✓ Itching, stinging, and burning between your toes or on soles on feet.
- ✓ Blisters on feet that itch.
- ✓ Cracking and peeling skin on feet, most commonly between toes and on soles.
- ✓ Dry skin on soles or sides of on feet
- ✓ Dis-colored, thick, and crumbly toenails.
- ✓ Toenails that pull away from the nail bed.

Treatments-

- ✓ Topical, prescription-strength clotrimazole or miconazole.
- ✓ Oral antifungal medications such as itraconazole (Sporanox), fluconazole (Diflucan), or prescription-strength terbinafine (Lamisil).
- ✓ Topical steroid medications to reduce painful inflammation and terbinafine.
- ✓ Oral antibiotics if bacterial infections develop due to raw skin and blisters[34].

b) Jock itch-

Tineacruris, sometimes known as jock itch, is a skin ailment caused by a fungus. Mold-like fungi known as dermatophytes cause jock itch, just like other tinea infections. These minute fungi can be found on the surface of your skin, hair, and nails.

They're usually innocuous, but if they're allowed to thrive in warm, damp environments, they can quickly reproduce and cause diseases. Because of this, jock itch most commonly affects the skin around the groin, inner thighs, and buttocks.

Symptoms-

- ✓ Redness
- ✓ persistent itching
- ✓ burning sensation
- ✓ flaking, peeling, or cracking skin
- ✓ rashthat gets worse with exercise or activity
- ✓ changes in skin colour
- ✓ Rash that doesn't improve, worsens, or spreads after using OTC hydrocortisone (anti-itch) cream.

Treatment-

- ✓ Topical medications include econazole (Ecoza) or oxiconazole (Oxistat).
- ✓ While oral medications include itraconazole (Sporanox) or fluconazole(Diflucan)[36].

c) Ring worm-

A fungal infection of the skin, ringworm is also known as dermatophytosis, dermatophyte infection, or tinea.The term "ringworm" is

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misleading because the infection is caused by a fungus, not a worm. The illness causes a lesion that looks like a worm in the shape of a ring, hence the name ringworm.Although ringworm is most commonly used to indicate tineacorporis (body ringworm), it can also be used to denote tinea infection in other places, such as tineacruris (The groin ringworm).

Symptoms-

- ✓ Red, itchy, or scaly patches, or raised areas of skin called plaques.
- ✓ Patches that develop blisters or pustules.
- ✓ Patches that may be redder on the outside edges or resemble a ring.
- ✓ Patches with edges that are defined and raised.

Treatment-

- ✓ Over-the-counter (OTC) medications and antifungal skin creams may be recommended for use as well.
- ✓ These products may contain clotrimazole, miconazole, terbinafine, or other related ingredients[37].

d) Yeast infection-

A vaginal yeast infection is a fungal infection that produces inflammation, discharge, and acute itching of the vaginal and vulva tissues. Vaginal yeast infection, also known as vaginal candidiasis, affects up to three out of every four women at some point in their lives. At least two episodes are common in many women.

Symptoms-

- ✓ Itching and irritation in the vagina and vulva.
- ✓ A burning sensation, especially during intercourse or while urinating.
- ✓ Redness and swelling of the vulva.
- ✓ Vaginal pain and soreness.
- ✓ Vaginal rash.

Treatment-

- ✓ Antifungal medications like tebinafine, luliconazolewhich are available as creams, ointments, tablets and suppositories include.Miconazole(Monistat 3).Terconazole[38].

e) Onchomycosis (nail-infection)-

Onychomycosis, often known as a fungal nail infection, occurs when fungus or yeast infect the fingernails or toenails. Nearly 50% of all nail diseases are caused by fungus. Fungus forms beneath the growing area of the nail and travels up the finger (proximally) along the nail bed and grooves on the sides of the nails in the most frequent form of fungal nail infections. A fungus can infect the nails at any age, although it is more common in adults, especially those who are older.

Symptoms-

- ✓ In some forms of fungal nail infection, black or white, powdery discoloration on the surface of the nail plate.
- ✓ In some forms of fungal nail infection, abnormal changes farther up the finger (proximally), where the nail originates.
- ✓ Fungal nail infection may occur in people with athlete's foot (tinea pedis) and/or oozing infection (paronychia), caused by inflammation and infection with yeast and/or bacteria in the region where the skin of the finger meets the origin of the nail.
- ✓ In fungal nail infection, one, a few, or all nails may be affected.

Treatment-

- ✓ The most commonly used agents are terbinafine, itraconazole, and fluconazole.
- ✓ In stubborn (refractory) fungal nail infection, surgical removal of part of the nail or the entire nail, removing the nail by applying a chemical, or thinning the nail by applying 40% urea ointment may be used, in addition topical or oral antifungal agents [27].

E) Pharmacodynamics property-

Terbinafine inhibits squaleneepoxidase, a membrane-bound enzyme system that isn't related to the cytochrome P-450 family [19]. In fungi, this results in a lack of ergosterol in the cell wall and a buildup of intracellular squalene. Terbinafine's in vitro fungicidal effect against most fungal diseases, including dermatophytes and dimorphic and filamentous fungi, may be due to this mechanism. The minimal inhibitory concentration (MIC) range for dermatophytes is 0.001 to 0.01 mg/L [29]. Terbinafine is fungicidal against Candida parapsilosis but fungistatic against Candida albicans when tested in vitro. The outer and inner layers of the arthroconidial cell wall may be the first targets of terbinafine activity, followed by changes in the cytosol and intracellular organelles. [30].This can produce an inhibitory effect on the morphologic transformation and invasiveness of dermatophytes.

F) Pharmacokinetic property-

Absorption- Terbinafine is highly absorbed (>70 percent) when taken orally, and this is not altered by diet. Terbinafine is a keratophilic and lipophilic compound [16]. Oral terbinafine (250 mg/day) has predictable pharmacokinetics in healthy volunteers and patients with onychomycosis, as characterised by a three-compartment model. Within 1.3 to 2

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hours, a single dosage of terbinafine 250 mg reaches peak plasma concentrations (Cmax) of 0.8 to 1.5 mg/L. (tmax). Concurrent meal consumption delayed tmax and slightly raised Cmax, resulting in a slightly enlarged area under the plasma concentration-time curve (AUC). A multiple-dosage regimen of terbinafine 250 mg/day improved Cmax values by 25% and AUC values by 2-fold in steady state in healthy volunteers and patients with onychomycosis [21].

Distribution-It may be found in adipose tissue, the dermis, the epidermis, and the nails[16]. Terbinafine is rapidly transported to the nail, stratum corneum, hair, and dermis epidermis, which are all weakly perfused tissues. Terbinafine concentrations in the nails are identified within one week of initiating medication and last for at least 30 weeks after treatment is completed [21]. The medication is widely dispersed throughout the body, with mean distribution volumes of 220.6 and 726.9L in the central and peripheral compartments, respectively [29].

Metabolism-Hepatic biotransformations of terbinafine, predominantly phase I oxidation processes, are considerable. The oxidised metabolites become more hydrophilic during Phase II conjugation processes, making them easier to eliminate by urine excretion. Terbinafine metabolism uses a portion of the hepatic cytochrome P450 (CYP) capacity compared to azole metabolism (>60 vs. 5%). After a single dosage, the terminal elimination half-life (t1/2) is less than the initial elimination half-life (t1/2 16 to 26 hours). In individuals given terbinafine 250 mg/day for four weeks, the t1/2 was 22 days. The majority of a terbinafine dosage is excreted in the urine (as metabolites), with the rest passing via the feces. In healthy participants, the total plasma clearance of terbinafine is 76 L/h..

Elimination-After a single dosage, the early elimination half-life (t1/2 16 to 26 hours) is less than the terminal elimination half-life (t1/2 90 hours). Patients who took 4 weeks of terbinafine 250 mg/day had a t1/2 of 22 days. The majority of a terbinafine dosage is excreted in the urine (as metabolites), with the remaining removed through the feces. Terbinafine had one total plasma clearance of 76 L/h in healthy individuals. [21].Terbinafine has a considerable affinity for plasma proteins such as albumin and lipoprotein fractions. Terbinafine is more slowly eliminated from adipose tissue than from other tissues due to its lipophilic characteristics. Breast milk is also secreted by the medication. Terbinafine undergoes significant hepatic metabolism and is largely eliminated in the urine (about 80% of a dosage), with the remaining passing through the feces. Terbinafine has a total plasma clearance of 75 L/h (1250 ml/min), and plasma elimination half-lives of II to 16 hours have been recorded after unlabeledterbinafine treatment, with an extra elimination phase of 90 to 100 hours after radiolabelled terbinafine administration.Terbinafine pharmacokinetics in old adults were similar to those in healthy young volunteers, although drug excretion was much slower in patients with compromised hepatic or renal function, resulting in significantly higher AUC values. Terbinafine penetrates the systemic circulation at a rate of less than 5% of dosage following topical treatment [29].

G) Mechanism of action-

Terbinafine inhibits the enzyme squalenemonooxygenase (also called squaleneepoxidase), preventing the conversion of squalene to 2,3-oxydosqualene, a step in the synthesis of ergosterol[19], [21]. This inhibition leads to decreased ergosterol, which would normally be incorporated into the cell wall, and accumulation of squalene[19].

Generation of a large number of squalene containing vesicles in the cytoplasm may leach other lipids away from, and further weaken, the cell wall [19].

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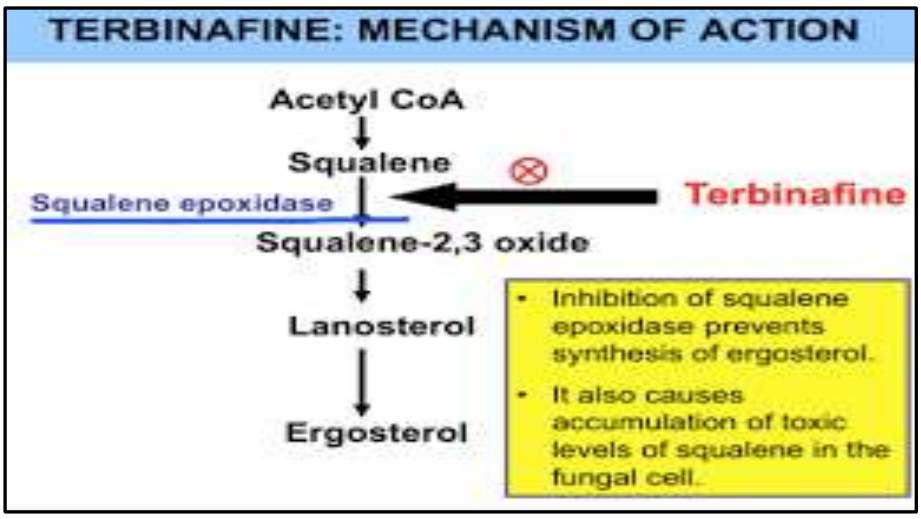

Fig A; Mechanism of terbinafine [35]

Dose-[39**,** 40]

A) For granules (oral dose form):

For tineacapitis (scalp fungal infections):

Adults- A typical dose is 250 milligrams (mg) once a day for six weeks.

Children aged 4 and above who weigh more than 35 (kg). The normal dose is 250 mg once a day for six weeks.

Children weighing 25 kg to 35 kg who are 4 years old or older. The normal dose is 187.5 mg once a day for six weeks.

Children who are 4 years old or older weigh less than 25 kilograms. The normal dose is 125 mg once a day for six weeks.

Doctors must determine the use and dose for children under the age of four**.**

B) For oral dosage form (Tablet):

For onychomycosis (fingernail fungus infections):

Adults: Take 250 mg once a day for 6 weeks.

Children's dosage and use must be determined by a physician.

For onychomycosis (toenail fungus infections):

Adults: Take 250 mg once a day for 12 weeks.

Children's dosage and use must be determined by a physician.

To treat tineacorporis (body ringworm), follow these steps:

250 milligrams (mg) once a day for 2 to 4 weeks for adults and teenagers.

Children's dosage and use must be determined by a physician.

For tineacruris (ringworm of the groin; jock itch):

Adults and teenagers: 250 milligrams (mg) once a day for 2 to 4 weeks for tineacruris (groin ringworm; jock itch).

Children's dosage and use must be determined by a physician.

Adults and teenagers: 250 mg once a day for 2 to 6 weeks for tinea pedis (ringworm of the foot; athlete's foot).

Children's dosage and use must be determined by a physician.

C) Topical dose-

For the treatment of tinea pedis.

Adults, adolescents, and children aged 12 and up, 1 % OTC spray or topical solution.

For one week, apply twice daily to the affected areas between the toes.

There hasn't been any research done on using it for tinea pedis on the bottom or sides of the feet.

At least once per day, change your shoes and socks.

Adults receive a topical dose of (1% prescription gel).

Apply once a day for one week to the affected regions and the surrounding skin. At least once per day, change your shoes and socks.

Topical dosage (1% OTC gel)

Adults, adolescents, and children over the age of 12 are all can apply.

For one week, apply to the affected regions between the toes once a day before sleep. There hasn't been any research done on using it for tinea pedis on the bottom or sides of the foot. At least once a day, change your shoes and socks.

Dosage on the skin (1% OTC cream).

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Adults, adolescents, and children over the age of 12 are can apply.
Apply twice daily to the affected areas. One week of treatment is recommended for tinea pedis between the toes. Treat tinea pedis on the bottom and sides of the foot for two weeks. At least once a day, change your shoes and socks.

For the treatment of tineacruris or tineacorporis.

Dosage on the skin (1% OTC spray, solution, gel, or cream).
Adults, adolescents, and children over the age of 12 are all eligible.
Apply once a day for a week to the affected areas.
Adults (1 % prescription gel)
Apply once a day for one week to the affected areas and surrounding skin.

I) Uses-

Onychomycosis and other dermatomycoses have been shown to respond well to oral terbinafine. Terbinafine may also be used to treat some systemic mycoses (such as chromomycosis) (Esterre et al., 1996). Terbinafine has been studied for the treatment of cutaneous dermatophyte and Candida infections, as well as pityriasisversicolor, as an oral (250 or 500 mg/day) or topical (50 mg/day) cream (1% twice daily). Oral terbinafine has also been investigated for the treatment of dermatophyte nail infections (Balfour and Faulds, 1992). It's used to treat ringworm, athlete's foot, and jock itch, among other fungal skin illnesses.It also aids in the relief of itching, burning, cracking, and scaling associated with these illnesses. (https://www.webmd.com/drugs/2/drug-166799/terbinafine-topical/details). Trichophyton (e.g. T.rubrum, T.mentagrophytes, T.verrucosum, T.violaceum), Microsporumcanis, and Epidermophytonfloccosum cause fungal infections of the skin and nails. Terbinafine tablets are used to treat these diseases [42].

The minimum inhibitory concentrations (MIC) for dermatophytes are included in the table below..

Organism	MIC rang (µg/ml)
Trichophytonrubrun	0.001 – 0.15
Trichophytonmentagrophytes	0.0001 – 0.05
Trichophytonverrucosum	0.001 – 0.006
Trichophytonviolaceum	0.001 – 0.1
Microsporumcanis	0.0001 – 0.1
Edidermorphytonfluccosum	0.001 – 0.05

Table B-outlines the range of minimum inhibitory concentrations (MIC) against the dermatophytes [42].

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