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A DESCRIPTIVE REVIEW ON PHARMACOKINETICS AND PHARMACODYNAMICS PROFILE OF ANANTIFUNGAL AGENT: CLOTRIMAZOLE

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ABSTRACT

Clotrimazole is marketed as a regularly occurring drug under numerous distinct names and via meansof numerous agencies because of its antifungal activity. Clotrimazole, an artificial imidazole derivative, is often used domestically for the remedy of vaginal and pores and skin infections because of yeasts and dermatophytes. It shows maximum activity towards Candida spp., Trichophyton spp., Microsporum spp. and Malazzesia furfur (Pityrosporon orbicular) in vitro. In addition, it also has a few in vitro towards Gram positive bacteria, and at very high concentrations shows activity towards Trichomonas spp. In the remedy of vaginal candidiasis, Clotrimazole vaginal pills have produced treatment costs similar with the ones of traditional nystatin vaginal pills. Clotrimazole has been a success in sufferers of non- responsive patients to different antifungal formulations together with nystatin and amphotericin B. Results in trichomonal vaginitis are not impressive. Skin infections because of Candida or dermatophytes had been successfully deals with topical use of clotrimazole. In comparative trials, clotrimazole cream has been as powerful as Whitfield's ointment and tolnaftate with inside the remedy of dermatophytoses , and as powerful as nystatin in cutaneous candidiasis. Clotrimazole topical formulations are well tolerated; however skin infection has withdrawal of remedy in some cases. Candida septicemia and urinary and pulmonary candidiasis had been cured with oral clotrimazole remedy. Results in different kinds of fungal infections, such as pulmonary aspergillosis, had been disappointing. A restricting issue in oral clotrimazole remedy is the excessive occurrence of gastro- intestinal disturbances and neurological reactions.

KEYWORDS: - Clotrimazole, Anti-fungal activity, Dermatophytoses, Vaginal pills, Microspore, Trichomonal vaginitis.

INTRODUCTION

A very exciting and attractive group of compounds appears to be complexes of Co (III) with diamine chelate ligands. The predominant characteristic permits the usage of complexes of cobalt (III) as an element of chemotherapeutic agents is the presence of stable Co (III) and labile Co (II). On the other hand, complexes of Co (II) are stable in solid form; however show off extremely good ease of oxidation beneath organic conditions. The antiviral, antibacterial, antitumor and antifungal activities of Co (II) and Co (III) coordination compounds have been broadly described.[42]

Candida spp., specifically Candida albicans, is one of the most important opportunistic fungal pathogens, which could harmlessly colonize the gastrointestinal tract, mouth, urogenital system and skin.[32] However, it additionally caused infections, especially amongst humans with weakened immune systems, attacking the pores and skin, mucous membranes, stepping into the blood, and attacking inner organs. Risk elements which are conducive to the improvement of systemic infections resulting from Candida include: long-time period live in extensive care units, surgery (especially operations with inside the belly cavity), broad-spectrum antibiotic intake, and immunosuppressant. [33] Antitumor chemotherapy, organ transplants, hemodialysis, parenteral nutrition, or venous catheters make a contribution to the invasion of fungi.[34] Other species of Candida an increasing isolated from sufferers are Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida krusei.[35]

Consequently, the listing of antifungal agents used presently in scientific remedy for the cure of infections because of limited candida (e.g., polyenes, azoles or echinocandins, currently taken into consideration due to most antifungal effect).[37]

Due to the quick listing of antifungal agents, efforts had been made to enhance the effectiveness or to lessen the toxicity of drugs, e.g., through acquiring a synergistic effect by the aggregate application of antifungals (e.g., the combination of fluconazole and amphotericin B). [40] Simultaneously completely new chemical substances

with an alternative mode of action, excessive antifungal activity and less toxicity are being sought. In the class of antifungals, amino acid biosynthesis inhibitors look like a completely promising group of compounds.[41]

A very exciting and attractive group of compounds appears to be complexes of Co (III) with diamine chelate ligands. The predominant characteristic permits the usage of complexes of cobalt (III) as an element of chemotherapeutic agents is the presence of stable Co (III) and labile Co (II). On the other hand, complexes of Co (II) are stable in solid form; however show off extremely good ease of oxidation beneath neath organic conditions. The antiviral, antibacterial, antitumor and antifungal activities of Co (II) and Co (III) coordination compounds have been broadly described. [42] Interestingly, the cobalt (III) complexes are also being investigated concerning their anticancer activity, such as the identity of cytostatic elements characterized with the aid of using study interactions with most cancers cells and really vulnerable outcomes on the body's healthy cells.[43] Two styles of coordination complexes [CoCl2(N,N)2]Cl, in which N,N is ethylenediamine or 1,3- diaminopropane because the chelating moiety, are the new variations of this class of chemical compound, and currently understanding approximately their organic interest is restricted to initial results. Recent literature concerning organic exams with coordination compounds of Co (III) with N,N-donor organic ligands has found out antibacterial and antifungal interest.[44]

In the existing studies, we decided the antifungal agents of Co (III) complexes with diamine chelate ligands in against to a huge variety of Candida spp. alone and in mixture with popular antifungal drugs. In addition, we tested the impact of compounds on fungal morphology and the mechanism of antifungal effect the using light and electron microscopy. We additionally carried out checks to evaluate the toxicity of Co (III) compounds.

Clotrimazole marketed under the brand name Lotrimin, amongst others, is an antifungal medication.[1] In 1960s, Clotrimazole was discovered as an imidazole antimycotic agent having four aromatic ringsin chemical structure, out of which one represents an imidazole ring. [4] As an active ingredient, worldwide it is marketed as a generic drug under different trade names.[11] Clotrimazole is the primary member of the triphenylmethane series of scientific importance. It has good *in-vitro* activity at very low concentrations towards a huge fungal variety (yeasts and molds).

However, hepatic enzymatic inactivation of this compound, after systemic administration, has restricted its use to topical applications (1% cream, lotion, solution, tincture, and vaginal cream) for superficial mycoses (nail, scalp, and skin infections) because of the dermatophytes and M. furfur, for preliminary and/or moderate oropharyngeal candidiasis (OPC; 10-mg oral troche), and for the intravaginal therapy (single utility of 500mg intravaginal tablet) of vulvovaginal candidiasis. Other intravaginal capsules require three to seven day applications. This drug is used for candidal stomatitis, dermatophytic infections, and nasal aspergillosis (infused via tubes) in dogs.[12]

More than 45 years ago, Canesten® was first registered clotrimazole in Germany.[5] Drug combinations (e.g., Clotrimazole + fluconazole) are also used nowadays. Clotrimazole monopreparations for the control of vulvovaginal candidiasis are to be had over-the-counter in maximum nations and covered a dose variety from 100 to 500 mg (strong systems). Comparable local Clotrimazole exposure may be performed through management of semi-strong systems (e.g., lotions containing Clotrimazole 1%, 2% or 10%) to the vagina and vulva.[4]

Clotrimazole has a poor oral bioavailability. When administered intravaginally, about 3% of the dose is systemically available.[6]

Common effects results while taken via means of mouth consist of nausea and itchiness. When implemented to the dermis, common side affects results redness and a burning sensation, but safe in pregnancy. There is no proof of damage while utilized by mouth at some point of being pregnant however this has been much less effectively studied. When utilized by mouth, extra care ought to be taken in people with liver problems.[1] It is the class of azole derivatives of medicinal drugs and worksvia disrupting the fungal mobileular membrane. It is on the World Health Organization's List of Essential Medicines.[3]

Approximately 70–75% of childbearing aged women affected symptomatic by vulvovaginal candidiasis once in their life duration and 40–50% will be afflicted by repeated episodes for the duration of their lifetime. About 5–8% of women can also additionally experienced recurrent vulvovaginal candidiasis (i.e., ≥4 episodes consistent with year). [7, 8] Clotrimazole resistance in vaginal candidiasis is uncommon and susceptibility testing is not usually advised.

Description[13,14,15]
Name: Clotrimazole
Appearance: white to pale yellow crystalline powder
Odor: Odorless
Molecular formula: C22H17Cl2 [16]
Molecular weight: 344.84g/mol[17]
Structure formula: Shown in fig 1

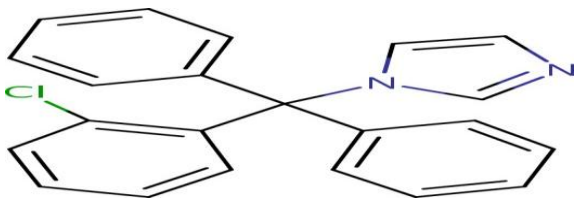

Fig. 1: Structure of clotrimazole.

IUPAC Name: 1-[(2-chlorophenyl)-diphenylmethyl] imidazole[18]
Melting point: 147-149 °C[19]
Category: antifungal medications called imidazole's[20]
Indications: oral candidiasis, vaginal candidiasis, and dermatomycoses[21,22,23]
Solubility: shown in table 1.1

Table 1.1 Solubility of clotrimazole in various solvents.[19]

Soluble	Acetone, Chloroform, Ethyl acetate
Slightly soluble	Water, Toluene, Benzene, Ether

Description of structural features
Clotrimazole is considerably to be chemically peculiar. It carries 4 aromatic rings bonded to a tetrahedral (sp3 hybridized) carbon atom, inflicting a fairly steric encumbrance in this atom. One of the aromatic groups is an imidazole ring, and that is regarded to mediate electron transfer reactions in organic systems (Eaton and Wilkins 1978; Eaton and Wilson 1979).[25,26] Its ultimate aromatic rings contain a triphenylmethyl system – a structure this is regarded to form and stabilize radical intermediates.[11, 27]

Out of which one ring is chloro-substituted at its C2 position. Although clotrimazole is an achiral molecule, its 2 phenyl rings are enantiotopic, with one being pro-R and the alternative pro-S. These enantiotopic specificities may be differentiated via means of interplay with a chiral molecule. [24, 28] Computational modeling of clotrimazole is a mechanically based on having 4 stable conformers,none of which 2 aromatic rings within the same plane.[29] These computational studies indicated thatthe energy content of a putative coplanar conformer could be very high, resulting in an incredibly unstable structure, because of interactions among the substituents on the ortho-positions within the aromatic rings. Thus, the authors concluded that clotrimazole does not have the coplanar physical properties which can be standard of many xenobiotics that act as ligands for the aryl hydrocarbon receptor; however substitute has a 'propeller-like' conformation. These computed models of clotrimazole's structure are supported via means of X-ray diffraction evaluation of the crystallineform of clotrimazole.[11,30]

Navas and co-workers additionally computed the molecular electrostatic potential (MEP) and dipole moment of clotrimazole. As those parameters offer an indication of the charge distribution and electrostatic potential of a molecule, they are used to model and provide an explanation of the interactions among biologically energetic chemical substances and their biomolecular targets. MEP mapping found out that clotrimazole possesses a peripheral electron-rich location similar to its nonsubstituted nitrogen atom and a region with a high quality electrostatic potential that corresponds to the substituted nitrogen atom.

This evaluation suggested that clotrimazole could interact efficaciously with acidic or electrophilic species which might be found in biological target molecules via its nonsubstituted nitrogen. Its dipole moment values were common in molecules with an excessive share of heteroatoms, low symmetry and comparatively big size. All four conformations of clotrimazole, the dipole orientates from the imidazole ring (terrible end) closer to the chlorine atom (high quality end) and dipole second values ranged from 3·78 to 5·58 D.[11]

Mechanism of action
Clotrimazole acts by destroying the permeability barrier inside the mobileular membrane of fungus. Clotrimazole causes inhibition of ergosterol biosynthesis which is an important constituent of fungal mobileular membranes. If ergosterol synthesis is either absolutely or partly inhibited, the mobileular is no longer able to construct an intact and functional cellular membrane. Because ergosterol can promotes the growth of fungal cell. Without any delay.

Though reduced ergosterol, because of the inhibition of lanosterol 14-demethylase (additionally called CYP51) is normal to be in most cases liable for the antimycotic properties of clotrimazole, thisdrug additionally indicates different pharmacological effects. It includes inhibition of sarcoplasmic reticulum Ca^{2+}-ATPase, depletion of intracellular calcium, and blocking of calcium dependent potassium channels and voltage-dependent calcium channels.[11, 97]

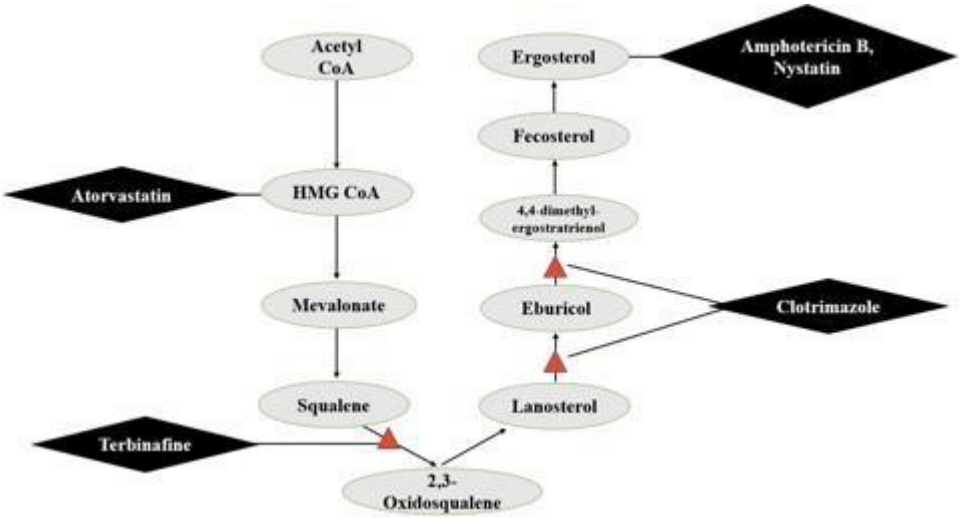

Fig. 2:- Ergosterol is a crucial factor of fungal plasma membranes pleasurable a comparable feature to cholesterol in animal mobileular membranes. Clotrimazole targets the enzyme lanosterol 14-*α*- demethylase accountable for the conversion of lanosterol to 4, 4-dimenthyl-ergostrienol a common target of azole drugs. Other antifungal drugs like terbinafine, targets squalene epoxidase.

Table 1.2:- Target sites for clotrimazole actions.

Target sites	Clotrimazole actions	Organisms
Cytochrome P450 51	Antagonist Inhibitor	Yeast
Intermediate Conductance calcium activated potassium channel protein 4	Inhibitor	Humans
Nuclear receptor subfamily 1 group member 2	Activator	Humans
Hydroxycarboxylic Acid receptor 2	Partial Agonist	Humans
Ergosterol	Inhibitor	Candida Albicans

Cytochrome P450- 51:-[113,114,115,116,97]
It is a form of protein located in yeast. Its molecular weight is 60674.965 Dalton Clotrimazole has a pharmacological activity of antagonist inhibitor on cytochrome P450 51. Cytochrome P450 51, function of sterol is 14-demethylase interest and Catalyzes C14-demethylation of lanosterol that is vital for ergosterol biosynthesis. It transforms lanosterol into 4,4'-dimethyl cholesta-8,14,24- triene-3-beta-ol.

Intermediate conductance calcium-activated potassium channel protein 4:- [117, 118, 119, 120]
It is a form of protein determined in humans. Its molecular weight is 47695.12 Dalton. Clotrimazole has a pharmacological gesture of inhibiting Intermediate conductance calcium activated potassium channel protein 4. This protein has a feature of protein phosphatase binding and forms a voltage unbiased potassium channel that is initiated with the aid of using intracellular calcium. Activation is follows membrane hyperpolarization which help in calcium influx.

Nuclear receptor subfamily 1 group member 2:[121,122,123,124]
It is a kind of protein found in humans. Its molecular weight is 49761.245 Dalton. Clotrimazole activate it. This protein has feature of nuclear receptor that binds and is activated via means of endogenous and xenobiotic compounds. Transcription factor that activates the transcription of more than one gene with inside the metabolism.

Hydroxycarboxylic acid receptor:[125, 126]
It is a kind of protein found in humans. Its molecular weight is 41849.08 Dalton. Clotrimazole act as partial agonist. This protein acts as an excessive affinity receptor for each nicotinic acid (additionally called niacin) and (D)-beta-hydroxybutyrate and mediates multiplied adiponectin secretion and reduced lipolysis.

Ergosterol: It is a small molecule determined in candida albicans. Clotrimazole acts as inhibitor to it.

Pharmacokinetics and Pharmacodynamics of Clotrimazole

Pharmacodynamics

Clotrimazole is an antifungal drug however it has effectiveness in most cancers treatment. Drug activity is primarily based on the inhibition of mitochondrial-bound glycolytic enzymes and calmodulin, which starves most cancers cells of energy. Clotrimazole and its derivatives were showing the lower costs of most cancers mobileular proliferation, result in g1 segment arrest, and promote pro-apoptotic factors, which cause mobileular death.[99]

Antifungal Spectrum: Blastomyces dermatitidis, Candida

spp, Coccidioides immitis, Cryptococcus neoformans, Dermatophytes (Trichophyton, Microsporum, Epidermophyton), Histoplasma capsulatum, Malassezia furfur, Naegleria fowleri, Nocardia spp, Paracoccidioides brasiliensis, Sporotrichum scenici.

Drug pharmacokinetics

Absorption: After oral drug administration has very bad oral bioavailability. Less than 3% is absorbed from mucosal surfaces and much less than 0.5% is absorbed via the skin.[112] Absorption is limited with topical administration of drug. Systemic drug administration is avoided. Administration of drug through oral/transmucosal routes occurs by dissolution of lozenzes (troche) inside the mouth, topical orintravaginal routes.

Time to peak, serum: a mean peak serum level, similar to only 0.03 µg equivalents/mL of Clotrimazole, turned into reached 1 to 2 days after application.

Oral, topical: Salivary ranges arise inside 3 hours after half-hour of dissolution time vaginalcream: High vaginal ranges take 8-24 hours.

Distribution: Distributed minimally with local utility with the aid of skin surface. When topically applied clotrimazole absorption in blood serum and tissues is very less to consider effective.

Metabolism: Most of the absorbed drug is metabolized on first pass through the liver as inactivatedcompound.

Excretion: Clotrimazole is mostly excreted via feaces and urine as metabolites and a small quantityof drug is excreted via bile. It is not recognized that it is excreted in human milk or not.[102, 103, 104]

Administration

Clotrimazole is not for systemic administration; it is administered through oral/transmucosal lozenges (troches), both topically or intravaginally. Small portions are absorbed and metabolized in the liver and excreted via bile.

Oral route

Transmucosal route - Clotrimazole oral lozenges are used for local cure and are not extensively bioavailable. Concentrations persisting in saliva appear because of clotrimazole binding to the oral mucosa.

Topical route

There is minimum systemic absorption following topical utility of clotrimazole.

Intravaginal route - more or less 5 to 10% of clotrimazole undergoes absorption following vaginal use. Therefore, fungicidal concentrations can persist inside the vagina for up to three days after application.[98]

Dosage forms [103]

Usual Adult Dose and Available by prescription only

Oral lozenges: 10 mg
Topical cream: 1% (15g, 30g, 45g, 90g)
Topical lotion: 1% (30 mL)
Topical solution: 1% (10 mL, 30 mL)
Vaginal tablets: 100 mg, 200 mg, 500 mg
Combination pack: Vaginal tablets 500 mg/topical cream 1% 7 g
Vaginal cream: 1% (45g, 90g), 2% (25g)
Vaginal tablets: 100 mg, 200 mg, 500ml

Table 1.3:- Clotrimazole formulations with brand Name and Concentrations.

S. no.	Drug Formulations	Concentration	Route of administration	Brand Name
1	Clotrimazole Cream	10mg/1gm	Topical	Lotrimin
2	Clotrimazole solution	10 mg/1mL	Topical	Lotrimin
3	Clotrimazole Troche	10 mg/1	Oral	Mycelex
4	Clotrimazole Troche	10 mg/1	Oral; Topical	Mycelex

Table 1.4:- Marketed Combination formulations of clotrimazole.

S. no.	Name of drug	Active ingredients	Formulation	Route of administration
1	Candacort Cream	Clotrimazole (1 % w/w) + Hydrocortisone (1 % w/w)	Cream	Topical
2	Canesoral combi	Clotrimazole (1 %) + Fluconazole (150 mg / cap)	Capsule, Cream	Oral; Topical; Vaginal
3	Candid-B Cream	mazole (1 % w/w) + Beclomethasone dipropionate (0.025 % w/w)	Cream	Topical
4	Alertrex	Clotrimazole (1 g) + Dexamethasone acetate (0.04 g) + Neomycin (0.5 g)	Cream	Topical
5	Baycuten N Crema	Clotrimazole (1 g) + Dexamethasone acetate (0.04 g) +	Cream	Topical

		Neomycin sulfate (0.5 g)		
6	Betamethasone lotrimazole	Clotrimazole (10 mg/1) + Betamethasone dipropionate (0.64 mg/1)	Cream	

Application of clotrimazole

Application in different type of clotrimazole preparations

1) **Clotrimazole cream: -** Clotrimazole cream is used to cure tinea corporis (ringworm; fungal spores and skin contamination that reasons a purple scaly rash on exceptional components of the body), tinea curries (jock itch; fungal contamination of the pores and skin with inside the groin or buttocks), and tinea pedals (athlete's foot; fungal contamination of the pores and skin at the toes and among the toes). Clotrimazole is in a category of antifungal medicines known as imidazole. It works with the aid of preventing the boom of fungi that reasons the contamination.
2) **Clotrimazole micro emulsion vaginal gels:-** Vaginal semisolids, especially gels primarily based on mucoadhesive polymers that are presently receiving a notable deal of hobby as vaginal transport structures.[149] The local (vaginal) transport now no longer most effective offers site-unique remedy however additionally avoids poisonous facet results of antifungal sellers which can be encountered on oral administration.[148]
3) **Clotrimazole dusting powder: -**It is used for the prevention of fungal infections on account of sweatand moisture accumulation. It offers remedy with inside the case of prickly warmness at the back, neck, and shoulder. In addition to this, it prevents itching in intimate frame parts, underarms, internal thighs,waistline, and feet.
4) **Clotrimazole lozenges: -** Lozenges are the flavored medicated dosage forms supposed to be sucked and held inside the mouth or pharynx containing one or greater medicaments normally with inside the sweetened base. Lozenges are supposed to relieve oropharyngeal symptoms, which can be normally induced by neighborhood infections and additionally for systemic impact supplied the drug is properly absorbed via the buccal linings or while it is swallowed.[150]

Drug-drug interactions

Clotrimazole is not extensively absorbed in blood stream, drug interactions are not a primary problem with its use. The topical form of drug is minimally absorbed inside the serum and tissues.

Table 1.5:- Drug-Drug interaction of clotrimazole.

Drug	Brand name	Interaction
Acenocoumarol	Acitrom	The therapeutic efficacy of acenocoumarol may be increasedwhile utilized in mixture with Clotrimazole.
Capmatinib	Tabrecta	The serum concentration of capmatinibmay be reduced while it is aggregate With clotrimazole.
Clindamycin	Deriva-c, acanya,cleocin,cle o c i n - t, clindacin, clindacure, clindagel	The metabolism of clindamycin maybe expanded when aggregate with clotrimazole
Dicoumarol	----------	The therapeutic efficacy of dicoumarol May be expanded when used in aggregation with clotrimazole.
Fluindione	Previscan	The therapeutic efficacy of fluindionemay beimproved when utilized in Aggregation with clotrimazole.
Lemborexant	Dayvigo	The serum concentration of lemborexant may be reduced while it is Mixed with clotrimazole.
Phenindione	Dindevan, fenindion	The therapeutic efficacy of phenindione May be improved while utilized in mixture with clotrimazole.
Phenprocoumon	Marcoumar, marcumar, falithrom	The therapeutic efficacy of phenprocoumon may be elevated whilst utilized in mixture wit Clotrimazole.
Rimegepant	Nurtec-odt	The metabolism of rimegepant may be

		Extended while mixed with clotrimazole.
Selpercatinib	Retevmo	The serum concentration of selpercatinib may be reduced while it is Aggregated with clotrimazole
irolimus	Rapacan, rapamune	The serum concentration of sirolimusmay be improved while it is mixed with Clotrimazole
Tacrolimus	Prograf	The serum concentration of Tacrolimus may be extended when it is
		Mixed with clotrimazole.
Warfarin	Coumadin, jentoven	The therapeutic efficacy of warfarinmay be expanded when utilized in Combination with clotrimazole
Tioclomarol	----------	The therapeutic efficacy of tioclomarol may be elevated when Utilized in mixture with clotrimazole
Amphotericin b	Amphotec, amphocil, fungilin,abelcet	Imidazoles (e.g., ketoconazole,miconazole, clotrimazole, fluconazole, etc.): in vitro and animal research with the mixture of amphotericin b and imidazoles recommend that imidazolescan also additionally set off fungalresistance to amphotericin B. Combination therapy must be administered with caution, particularly in Immunocompromised Patients.

Contraindications[106]

Clotrimazole have now no longer been used for systemic fungal infections due to poor oral absorption.

Onychomycosis:- As with many different topical antifungal drugs, topical clotrimazole is not powerful for onychomycosis. This condition usually requires cure with an oral (systemic) antifungaldrug.

- **Azole antifungals hypersensitivity: -** Clotrimazole should be used with warning in patients with azole antifungals hypersensitivity. Hypersensitivity reactions can be due of the diverse vehicles present in the distinct clotrimazole formulations. Clotrimazole can also cross sensitivity with different azole derivatives.
- **Abdominal pain, diabetes mellitus, fever, human immunodeficiency virus (HIV) infection, and immunosuppression, vaginal discharge:-** Self-administration of clotrimazole for longer than 7 days is contraindicated. If there is no upgrade in the circumstance after three days, or if the circumstance persists after 7 days, the affected person should stop clotrimazole remedy and seek advice from a physician. Some patients should no longer use non-prescription clotrimazole products without the supervision of a fitness care expert; sufferers with immunosuppression, undergoing chemotherapy, diabetes mellitus, or human immunodeficiency virus (HIV) infection should discuss the use of those products with their fitness care expert previous to self-treatment. Females should no longer self-deal with intravaginal clotrimazole products if the subsequent symptoms and signs are present: belly pain, fever > 100º F, or foul-smelling vaginal discharge. Such signs and symptoms can be an illustration of some other vaginal infection or pelvic inflammatory disease. Approximately 20% of all vaginal candida infections co-exist with some other infection.
- **Ocular exposure, ophthalmic administration:-** Avoid ocular exposure to clotrimazole; do not longer provide with the aid of using ophthalmic administration. If ocular exposures occur, deal with the aid of using instant flushing the affected eyewith cool, clean water. Contact an ophthalmologist if eye inflammation persists.

Clotrimazole and Pregnancy

The FDA categorizes medicines primarily based on protection to be used for the duration of pregnancy. Five categories - A, B, C, D, and X, are used to categories the possible dangers to an unborn baby meanwhile a medicinal drug is taken for the duration of pregnancy.

Topical clotrimazole cream and solutions fall into class B. In animal research, pregnant animals have been given clotrimazole, and a few infants had troubles. But in human research, pregnant ladies have been given this medicinal drug and their infants did not longer have any troubles associated with this medication. Clotrimazole lozenges fall into class C.

Clotrimazole indicates poor absorption after dermal or intravaginal administration. Only topical arrangements are approved in pregnant.[106] Because clotrimazole has negative oral bioavailability, it is not likely to adversely ha effect on the breastfed infant, which includes topical application to the nipples. It has been used orally in infants with thrush, sometimes effectively after nystatin has failed.

There are insufficient well-controlled human studies using topical or intravaginal clotrimazole for the duration of the primary trimester of pregnant clotrimazole should

only simplest be used if indicated. [101, 106] In medical trials, vaginal use for the duration of the second and third trimesters in human beings has now no longer results in any damaging consequences; there are no good enough and well-managed research of pregnant ladies for the duration of the primary trimester. Use topical or vaginal clotrimazole for the duration of the primary trimester of being pregnant simplest if actually indicated. In animal research, no fetal damage happened after intravaginal doses as much as 100 mg/kg in pregnant rats. Clotrimazole oral lozenges are categorized as FDA being pregnant class C. There are not inadequate and well-managed studies of oral clotrimazole in pregnant ladies. No teratogenicity consequences were validated in animal research at doses as much as 200 instances the human dose; But doses of one hundred instances the grownup human dose have been embryotoxic in rats and mice. Use oral clotrimazole lozenges for the duration of pregnant simplest if the ability advantage justifies the ability chance to the fetus.

Breast-feeding

The use of clotrimazole in the course of breast-feeding has been no longer studied. Topical software is not always predicted to bring about substantial maternal absorption, and should not be a substantial threat to a breast-feeding little one. Instruct moms now no longer to use clotrimazole topically to the breast in the course of instances of breast-feeding. The oral troches can be absorbed systemically, however substantial little one exposure is unknown and predicted to be low; study the little one for any feasible damaging effects. Fluconazole, miconazole, and nystatin can be potential options to consider, though site of infection, locally susceptibility patterns, and unique microbial susceptibility have to be assessed earlier than deciding on an alternating agent. Consider the privilege of breast- feeding, the threat of ability infant's drug exposure, and the threat of an untreated or inadequately cured condition. If breast-feeding infants reviews a damaging impact associated with a maternally ingested or administered drug, fitness care companies are advocated to report the damaging impact to the FDA.[105,106]

Contraceptive devices, Menstruation

Patients who use of intravaginal clotrimazole formulations are suggested to abstain from sexual sex at some point of the cure course. Contraceptive devices like condoms, diaphragms, and cervical caps may be broken as the use of those products, and might result in contraceptive failures. Although clotrimazole can be used in menstruation, instruct patients no longer to use tampons.

Adverse reactions

GI: Nausea, vomiting, unpleasant mouth sensation (with lozenges); lower abdominal cramps.
GU: Mild vaginal burning or irritation (with vaginal use), cramping, urinary frequency.
Skin: Blistering, erythema, edema, pruritus, burning, stinging, peeling, urticarial, skin fissures, general irritation. [103]

Overdose[111]

No danger of acute intoxication is visible as it is not likely to arise following a single dermal application of an overdose (application over massive vicinity below situations beneficial to absorption) or inadvertent oral ingestion. There is no particular antidote. However, In the occasion of unintended oral ingestion, ordinary measures like gastric lavage need to be done most effective if scientific signs and symptoms of overdose emerge as apparent (e.g. dizziness, nausea or vomiting). Gastric lavage need to be done most effective if the airway may be covered adequately.

Table 1.6:- Recent trends on clotrimazole.

S. no	Formulation	Strength	Year of Marketing	Marketed by
1	Clotrimazole topical solution,USP 1%	10mg/1ml	2019	Tasman Pharma.Inc
2	Clotrimazole topical solution ,USP,1%	10Mg/1ml	2019	TruPharma.Llc
3	Clotrimazole topical solution ,USP,1%	10mg/1ml	2019	Novitium Pharma Llc
4	Clotrimazole antifungal liquid dosage form	1g/100ml	2017	Guagzhou Ertiantang Pharmaceutical CO.Ltd
5	Clotrimazole anti-uid dosageform	10mg/1ml	2017	hern Sales andService,Inc
6	Clotrimazole antifungal cream	1g/100g	2020	Bluepoint Laboratories
7	Athlete foot cream with clotrimazole	1g/100g	2016	Sabel Med lcc
8	Athlete foot cream	10mg/1g	2018	Fred's,Inc
9	Candid cream 1% w/w	1%w/w	2020	Glenmark pharmaceuticals

REFERENCES

1. *American Society of Health-System Pharmacists "Clotrimazole Monograph for Professionals".* www.drugs.com *(8 February 2016).*
2. World Health Organization *(2019). World Health Organization model list of essential medicines, 2019; 21. Geneva: World Health Organization.* hdl*:*10665/325771. *WHO/MVP/EMP/IAU/2019.06. License: CC BY-NC-SA 3.0 IGO*
3. Mendling W, Atef El Shazly M, Zhang L. Clotrimazole for Vulvovaginal Candidosis: More Than 45 Years of Clinical Experience. Pharmaceuticals (Basel), 2020; 25; 13(10): 274.
4. Crowley PD and Gallagher HC: Clotrimazole as a pharmaceutical: Past, present and future. J. Appl. Microbiol, 2014; 117: 611–617.
5. Mendling W, Stock I, Becker N: Therapie von Vulvovaginalmykosen im Wandel der Zeit(Teil 2): Behandlungsprinzipien in der Antimykotikatherapie. Gyne, 2014; 35: 26–31.
6. Benziger DP, Edelson J: Absorption from the vagina. Drug Metab. Rev, 1983; 14: 137–168.
7. Sobel JD: Vulvovaginal candidosis. Lancet, 2007; 369: 1961–1971.
8. Jeanmonod R, Jeanmonod D: Vaginal candidiasis (vulvovaginal candidiasis). In StatPearls Treasure Island (FL); StatPearls Publishing: Treasure Island, FL. USA, 2020; 1–4.
9. Mendling W, Brasch J, Cornely OA, Effendy I, Friese K, Ginter-Hanselmayer, G , et al. Guideline: Vulvovaginal candidosis (AWMF 015/072), S2k (excluding chronic mucocutaneous candidosis). Mycoses 2015; 58: 1–15.
10. Mukasa KJ, Herbert I, Daniel A, Sserunkuma KL, Joel B: Antifungal susceptibility patterns of vulvovaginal candida species among women attending antenatal clinic at Mbarara regional referral hospital, South Western Uganda. Br. Microbiol. Res. J., 2015; 5: 0322–331.
11. Crowley PD and Gallagher HC: Clotrimazole as a pharmaceutical: Past, present and future. J. Appl. Microbiol, 2014; 117: 611–617.
12. Espinel-Ingroff, in Encyclopedia of Microbiology, 2009.
13. National Center for Biotechnology Information, PubChem Compound Summary for CID 2812, Clotrimazole. Retrieved December, 2021; 30.
14. Reynolds JEF, PrasadA.B. (eds.) Martindale, The Extra Pharmacopoeia. 28th ed. London, The Pharmaceutical Press, 1982; 721.
15. McEvoy, G.K. AHFS Drug Information 90. Bethesda, MD: American Society of Hospital Pha rmacists, Inc, 1990; 199: 2101).
16. Greenberg HL, Shwayder TA, Bieszk N, Fivenson DP: Clotrimazole/ betamethasone diproprionate: a review of costs and complications in the treatment of common cutaneous fungal infections. Pediatr Dermatol, 2002; 19: 78–81.
17. Czerninski R, Pikovsky A, Gati I, Friedman M, Steinberg D, Comparison of the efficacy of a novel sustained release clotrimazole varnish and clotrimazole troches for the treatment of oral candidiasis. Clin Oral Investing, 2014.
18. Buckner FS, Urbina JA: Recent Developments in Sterol 14-demethylase Inhibitors for Chagas Disease. Int J Parasitol Drugs Drug Resist, 2012; 2: 236–242.
19. Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989; 378.
20. Song H, Shin HS: The antifungal drug clotrimazole. Acta Crystallographica Section C: Crystal Structure Communications, 1998; 54(11): 1675-1677.
21. Kobayashi T, Amenomori Y: Results of a Clinical Investigation of Clotrimazole (Canesten), A New Anti-Mycotic Substance, in the Therapy of Vaginal Fungal Infections. *Journal of International Medical Research*, 1974; *2*(5): 366-369.
22. Woo TE, Somayaji R, Haber RM, Parsons L: Diagnosis and Management of Cutaneous Tinea Infections. Adv Skin Wound Care, 2019; 32(8): 350-357.
23. Kalra MG, Higgins KE, Kinney BS. Intertrigo and secondary skin infections. Am Fam Physician, 2014; 89(7): 569-73.
24. Martindale, The Extra Pharmacopoeia, July, Reprinted June 1979, Published by The Pharmaceutical Press, lambert high street, 1977; 21: SE: 643-644.
25. Eaton DR, Wilkins RG: Reduction by dithionite ion of adducts of metmyoglobin with imidazole, pyridine, and derivatives. J Biol Chem, 1978; 253: 908–915.
26. Eaton D, Wilson K: Reaction of imidazole and hydroquinone with oxymyoglobin. J Inorg Biochem. 1979; 10: 195–203.
27. Hicks RG: What's new in stable radical chemistry? Org Biomol Chem, 2007; 5: 1321– 1338.
28. Eliel EL, Wilen SH, Mander LN: Stereochemistry of organic compounds. New York: John Wiley and Sons, 1994; 381.
29. Navas JM, Chana A, Herradón B, Segner H. Induction of cytochrome P4501A (CYP1A) by clotrimazole, a non-planar aromatic compound. Computational studies on structural features of clotrimazole and related imidazole derivatives. Life Sci, 2004; 76: 699–714.
30. Song H, Shin HS. The antifungal drug clotrimazole. Acta Crystallography Section C: Crystal Structre Commun. 1998; 54: 1675–1677.
31. Katarzyna T, Agnieszka C, Anna K, Krzysztof F. Waleron Action of the Co(III) Coordination Complexes With Diamine Chelate Ligands Against Reference and Clinical Strains of *Candida*, 2018; 9: 1594.
32. Naglik JR, Moyes DL, Wächtler B, Hube B: Candida albicans interactions with epithelial cells and mucosal immunity. Microbes Infect, 2011; 13;

963–976.
33. Sydnor ERM, Perl TM: Hospital epidemiology and infection control in acute-care settings. Clin. Microbiol, 2011; 24: 141–173.
34. Mikulska M, Del Bono V, Ratto S, Viscoli C: (2012). Occurrence, presentation and treatment of candidemia. Expert Rev. Clin. Immunol, 2012; 8: 755–765.
35. MacCallum DM: Hosting infection: experimental models to assay Candida virulence. Int. J. Microbiol, 2012; 363764.
36. Roemer T, Krysan DJ: Antifungal drug development: challenges, unmet clinical needs, and new approaches. Cold Spring Harb. Perspect. Med, 2014; 4: a019703:
37. Ngo HX, Garneau-Tsodikova S, Green KD: A complex game of hide and seek: the search for new antifungals. Med. Chem. Commun. 2016; 7: 1285–1306.
38. Kuhn DM, Ghannoum MA: Candida biofilms: antifungal resistance and emerging therapeutic options. Curr. Opin. Investig. Drugs, 2004; 5: 186–197.
39. Odds FC: Fluconazole plus amphotericin B combinations are not contraindicated and may add benefit for the treatment of candidemia. Clin. Infect. Dis., 2003; 36: 1229–1231.
40. Jastrzębowska K, Gabriel I: Inhibitors of amino acids biosynthesis as antifungal agents. Amino Acids, 2015; 47: 227–249.
41. Dachs GU, Tozer GM: Hypoxia modulated gene expression: angiogenesis, metastasis and therapeutic exploitation. Eur. J. Cancer, 2000; 36: 1649–1660.
42. Chylewska A, Turecka K, Dąbrowska A, Werel W, Chmurzyński L: (2013). Synthesis, physicochemical characterization and antimicrobial activity of Co (III) complexes with diamine chelate ligands. IJAPBC, 2013; 2: 454–464.
43. Alsterholm M, Karami N, Faergemann J: (2010) Antimicrobial activity of topical skin pharmaceuticals – an in vitro study. *Acta Derm Venereol*, 2010; 90: 239– 245.
44. Bartolommei G, Tadini-Buoninsegni F, Hua S, Moncelli MR, Inesi G, Guidelli R: Clotrimazole inhibits the Ca2+-ATPase (SERCA) by interfering with Ca2+ binding and favoring the E2 conformation. *J Biol Chem*, 2006; 281: 9547– 9551.
45. Benzaquen LR, Brugnara C, Byers HR, Gattoni-Celli S, Halperin JA: Clotrimazole inhibits cell proliferation in vitro and in vivo. *Nat Med*. 1995; 1: 534– 540.
46. Bilensoy E, Rouf M, Vural I, Hincal A: Thermosensitive vaginal gel formulation for the controlled release of clotrimazole via complexation to beta-cyclodextrin. *J Control Release*, 2006; 116: 107– 109.
47. Brugnara C, De Franceschi L: Clinical trials of new therapeutic pharmacology for sickle cell disease. *Sante*, 2006; 16: 263– 268.
48. Brugnara C, Gee B, Armsby CC, Kurth S, Sakamoto M, Rifai N, Alper SL and Platt OS: Therapy with oral clotrimazole induces inhibition of the Gardos channel and reduction of erythrocyte dehydration in patients with sickle cell disease. *J Clin Invest*, 1996; 97: 1227– 1234.
49. Costa C, Nunes J, Henriques A, Mira NP, Nakayama H, Chibana H and Teixeira MC: *Candida glabrata* drug: H+ antiporter CgTpo3 (ORF CAGL0I10384g): role in azole drug resistance and polyamine homeostasis. *J Antimicrob Chemother*. 2014.
50. Cudmore SL, Delgaty KL, Hayward-McClelland SF, Petrin DP and Garber GE: Treatment of infections caused by metronidazole-resistant *Trichomonas vaginalis*. *Clin Microbiol Rev*, 2004; 17: 783– 793.
51. Eaton DR, Wilkins RG: Reduction by dithionite ion of adducts of metmyoglobin with imidazole, pyridine, and derivatives. *J Biol Chem*. 1978; 253: 908– 915.
52. Eaton D, Wilson K: Reaction of imidazole and hydroquinone with oxymyoglobin. *J Inorg Biochem*, 1979; 10: 195– 203.
53. Eliel, E.L., Wilen, S.H. and Mander, L.N. *Stereochemistry of organic compounds*. New York: John Wiley and Sons, 1994; 381.
54. Ellepola A, Samaranayake L: Oral candidal infections and antimycotics. *Crit Rev Oral Biol Med*, 2000; 11: 172– 198.
55. Gbotosho OT, Cytlak UM, Hannemann A, Rees DC, Tewari S and Gibson JS: Inhibitors of second messenger pathways and Ca-induced exposure of phosphatidylserine in red blood cellsof patients with sickle cell disease.2013
56. Gelone SA and O'Donnell J: Anti infectives. In *Remington the science and practice of pharmacy*, 21st Edition ed. D.B. Troy, 2006; 1626– 1684.
57. Gemma S, Campiani G, Butini S, Kukreja G, Joshi BP, Persico M, Catalanotti B, Novellino E: Design and synthesis of potent antimalarial agents based on clotrimazole scaffold: exploring an innovative pharmacophore. *J Med Chem*, 2007; 50: 595– 598.
58. Gemma S, Campiani G, Butini S, Kukreja G, Coccone SS, Joshi BP, Persico M, Nacci V: Clotrimazole scaffold as an innovative pharmacophore towards potent antimalarial agents: design, synthesis, and biological and structure–activity relationship studies. *J Med Chem*, 2008; 51: 1278– 1294.
59. Hicks, R.G. What's new in stable radical chemistry? *Org Biomol Chem*, 2007; 5: 1321– 1338.
60. Hitchcock CA, Dickinson K, Brown S, Evans E, Adams D: Interaction of azole antifungal antibiotics with cytochrome P-450-dependent 14 alpha-sterol demethylase purified from *Candida albicans*. *Biochem J*., 1990; 266: 475– 480.
61. Jan CR, Tseng CJ, Chou KJ, Chiang HT: Novel effects of clotrimazole on Ca^{2+} signaling in Madin Darby canine kidney cells. *Life Sci*, 2000; 66: 2289–2296.
62. Kalb, R. and Grossman, M. Contact dermatitis to

clotrimazole. Cutis, 1985; 36: 240– 242.
63. Lorand T, Kocsis B: Recent advances in antifungal agents. *Mini-Rev Med Chem*, 2007; 7: 900– 911.
64. Malani AN, Kauffman CA: Changing epidemiology of rare mould infections. *Drugs*, 2001\7; 67: 1803– 1812.
65. Marichal P, Gorrens J, Coene M: Biochemical basis for the activity and selectivity of oral antifungal drugs. *Br J Clin Pract Suppl*, 1990; 71: 41– 46.
66. Mishra N, Prasad T, Sharma N, Payasi A, Prasad R, Gupta D, Singh R: Pathogenicity and drug resistance in *Candida albicans* and other yeast species. *Acta Microbiol Immunol Hung*, 2007; 54: 201– 235.
67. Navarro M, Peña NP, Colmenares I, González T, Arsenak M, Taylor P: Synthesis and characterization of new palladium–clotrimazole and palladium–chloroquine complexes showing cytotoxicity for tumor cell lines in vitro. *J Inorg Biochem*, 2006; 100: 152– 157.
68. Navarro M, Higuera-Padilla AR, Arsenak M, Taylor P: (2009) Synthesis, characterization, DNA interaction studies and anticancer activity of platinum–clotrimazole complexes. *Transition Met Chem*, 2009; 34: 869– 875.
69. Navas JM, Chana A, Herradón B, Segner H: Induction of cytochrome P4501A (CYP1A) by clotrimazole, a non-planar aromatic compound. Computational studies on structural features of clotrimazole and related imidazole derivatives. *Life Sci*, 2004; 76: 699– 714.
70. Odds FC, Brown AJ, Gow NA: Antifungal agents: mechanisms of action. *Trends Microbiol*, 2003; 11: 272– 279.
71. OSPAR Commission (2005) Hazardous Substance Series: Open background documentation on clotrimazole; publication no, 2005; 199.
72. Oyama TM, Oyama TB, Oyama K, Matsui H, Horimoto K, Nishimura Y, Oyama Y: (2006) Clotrimazole, an antifungal drug possessing diverse actions, increases the vulnerability to cadmium in lymphocytes dissociated from rat thymus. *Toxicology*, 2006; 228: 269– 279.
73. Pasqualotto AC, Thiele KO, Goldani LZ: Novel triazole antifungal drugs: focus on isavuconazole, ravuconazole and albaconazole. *Curr Opin Investig Drugs*, 2010; 11: 165– 174.
74. Pelletier R, Peter J, Antin C, Gonzalez C, Wood L, Walsh TJ: Emergence of resistance of *Candida albicans* to clotrimazole in human immunodeficiency virus-infected children: in vitro and clinical correlations. *J Clin Microbiol*, 2000; 38: 1563– 1568.
75. Podust LM, Poulos TL, Waterman MR: Crystal structure of cytochrome P450 14α-sterol demethylase (CYP51) from *Mycobacterium tuberculosis* in complex with azole inhibitors. *Proc Natl Acad Sci*, 2001; 98: 3068– 3073.
76. Porsbring T, Blanck H, Tjellström H, Backhaus T: The pharmaceutical clotrimazole affects marine microalgal communities at picomolar concentrations. In *SETAC Europe 19th Annual Meeting, Gothenburg, Sweden*, 2009.
77. Rittenhouse A, Vandorpe D, Brugnara C, Alper S: The antifungal imidazole clotrimazole and its major in vivo metabolite are potent blockers of the calcium-activated potassium channel in murine erythroleukemia cells. *J Membr Biol*, 1997; 157: 177– 191.
78. Robles-Escajeda E, Martínez A, Varela-Ramirez A, Sánchez-Delgado RA, Aguilera RJ: Analysis of the cytotoxic effects of ruthenium–ketoconazole and ruthenium–clotrimazole complexes on cancer cells. *Cell Biol Toxicol*, 2013; 29: 431– 443.
79. Santos SS, Lorenzoni A, Pegoraro NS, Denardi LB, Alve SH, Schaffazick SR, Cruz L: Formulation and in vitro evaluation of coconut oil-core cationic nanocapsules intended for vaginal delivery of clotrimazole. *Colloids Surf B Biointerfaces*, 2014; 116: 270– 276.
80. Shah M, Miscony Z, Javadzadeh-Tabatabaie M, Ganellin C, Haylett D: analogues: effective blockers of the slow afterhyperpolarization in cultured rat hippocampal pyramidal neurones. *Br J Pharmacol*, 2001; 132: 889– 898.
81. Singh S, Jain S, Muthu M, Tiwari S, Tilak R: (2008) Preparation and evaluation of buccal bioadhesive films containing clotrimazole. *AAPS PharmSciTech*, 2008; 9: 660– 667.
82. Sobel JD: Vulvovaginal candidosis. *Lancet*, 2007; 369: 1961– 1971.
83. Song H, Shin HS: The antifungal drug clotrimazole. *Acta Crystallogr Sect C: Cryst Struct Commun*, 1998; 54: 1675– 1677.
84. Sweetman SC: *Martindale: the complete drug reference*. London: Pharmaceutical Press, 2007; 764.
85. Thapa D, Lee JS, Park MA, Cho MY, Park YJ, Choi HG, Jeong TC, Kim JA: Inhibitory effects of clotrimazole on TNF-α-induced adhesion molecule expression and angiogenesis. *Arch Pharm Res*, 2009; 32: 593– 603.
86. Tian M, Dong MQ, Chiu SW, Lau CP, Li GR: Effects of the antifungal antibiotic clotrimazole on human cardiac repolarization potassium currents. *Br J Pharmacol*, 2006; 147: 289– 297.
87. Tiffert T, Ginsburg H, Krugliak M, Elford BC, Lew VL: Potent antimalarial activity of clotrimazole in in vitro cultures of Plasmodium falciparum. *Proc Natl Acad Sci*, 2000; 97: 331– 336.
88. Tonglairoum P, Ngawhirunpat T, Rojanarata T, Kaomongkolgit R, Opanasopit P: Fast-acting clotrimazole composited PVP/HPbetaCD nanofibers for oral candidiasis application. *Pharm Res*, 2014.
89. Trivedi V, Chand P, Srivastava K, Puri SK, Maulik PR, Bandyopadhyay U: Clotrimazole inhibits hemoperoxidase of *Plasmodium falciparum* and induces oxidative stress. Proposed antimalarial mechanism of clotrimazole. *J Biol Chem*, 2005; 280: 41129– 41136.

90. Valerio C, Perillo T, Brescia L, Russo F: Antifungal agents in current pediatric practice. *Curr Infect Dis Rep*, 2013; 15: 278– 287.
91. Vanic Z, Skalko-Basnet N: Nanopharmaceuticals for improved topical vaginal therapy: can they deliver? *Eur J Pharm Sci*, 2013; 50: 29– 41.
92. Weig M, Brown AJ: Genomics and the development of new diagnostics and anti-Candida drugs. *Trends Microbiol*, 2007; 15: 310– 317.
93. White TC, Holleman S, Dy F, Mirels LF, Stevens DA: Resistance mechanisms in clinical isolates of *Candida albicans*. *Antimicrob Agents Chemother*, 2002; 46: 1704– 1713.
94. Wu SN, Li HF, Jan CR, Shen AY: Inhibition of Ca^{2+} activated K^{+} current by clotrimazole in rat anterior pituitary GH^{3} cells. *Neuropharmacology*, 1999; 38: 979– 989.
95. Plempel M: On the Action Kinetics of Clotrimazole. *Chemotherapy*, 1982; *28*(1): 22-31.
96. Haller I: Mode of action of clotrimazole: implications for therapy. American journal of obstetrics and gynecology. 1985
97. S, K: Clotrimazole as a Cancer Drug:A Short Review. *Medicinal Chemistry*, 2014; *4*(11).
98. Moudgal VV, Sobel JD: Antifungal drugs in pregnancy: a review. *Expert opinion on drug safety*, 2003; *2*(5): 475-483.
99. Johnstone HA, Marcinak JF: Candidiasis in the breastfeeding mother and infant. J Obstet Gynecol Neonatal Nurs, 1990;19:171-3
100. Noti A, Grob K, Biedermann M: Exposure of babies to C(15)-C(45) mineral paraffins from human milk and breast salves. Regul Toxicol Pharmacol, 2003; 38: 317-25.
101. Hoogerheide JG, Wyka B E: (1982). Clotrimazole. In *Analytical profiles of drug substances*, 1982; 11: 225-255.
102. Rifai N, Sakamoto M, Law T, Platt O, Mikati M, Armsby CC, Brugnara C: (1995). HPLC measurement, blood distribution, and pharmacokinetics of oral clotrimazole, potentially useful antisickling agent. *Clinical chemistry*, 1995; *41*(3): 387-391.
103. Njok JC, Gumeel D, Hermsen E D: Antifungal therapy in pregnancy and breastfeeding. *Current Fungal Infection Reports*, 2010; 4(2): 62-69.
104. Khatter NJ, Khan MAB: Clotrimazole. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2021.
105. Spencer JP, Gonzalez LS 3rd, Barnhart DJ, Medications in the breast-feeding mother. American family physician, 2001.
106. Van Schalkwyk J, Yudin MH, Vulvovaginitis: screening for and management of trichomoniasis, vulvovaginal candidiasis, and bacterial vaginosis. Journal of obstetrics and gynaecology Canada: JOGC = Journal d'obstetrique et al gynecologie du Canada: JOGC, 2015.
107. Black RA, Hill DA, Over-the-counter medications in pregnancy. American family physician, 2003; 15. [PubMed PMID: 12825840]
108. Yogeshwari P., Sriram D.,"Medicinal Chemistry" edition 2nd, published by Dorling Kindersley(India Pvt. Ltd), 498-499
109. Koch, S., Torres, S., & Plumb, D. Clotrimazole. Drug Therapy for Infectious Diseases of the Dog and Cat, 2015; 226.
110. Carlton K.K. Lee PharmD, MPH Harriet Lane Handbook, Chapter, 30, 665-1076
111. Warrilow AG, Martel CM, Parker JE, Melo N, Lamb DC, Nes WD, Kelly DE, Kelly SL: Azole binding properties of Candida albicans sterol 14-alpha demethylase (CaCYP51). Antimicrob Agents Chemother. 2010; 54(10): 4235-45.
112. Gachotte D, Pierson CA, Lees ND, Barbuch R, Koegel C, Bard M: A yeast sterol auxotroph (erg25) is rescued by addition of azole antifungals and reduced levels of heme. Proc Natl Acad Sci U S A., 1997; 14; 94(21): 11173-8.
113. Henry KW, Nickels JT, Edlind TD: Upregulation of ERG genes in Candida species by azoles and other sterol biosynthesis inhibitors. Antimicrob Agents Chemother. 2000; 44(10): 2693- 700.
114. Lorenz RT, Parks LW: Physiological effects of fenpropimorph on wild-type Saccharomyces cerevisiae and fenpropimorph-resistant mutants. Antimicrob Agents Chemother, 1991; 35(8): 1532-7.
115. Warrilow AG, Martel CM, Parker JE, Melo N, Lamb DC, Nes WD, Kelly DE, Kelly SL: Azole binding properties of Candida albicans sterol 14-alpha demethylase (CaCYP51). Antimicrob Agents Chemother. 2010; 54(10): 4235-45.
116. Gachotte D, Pierson CA, Lees ND, Barbuch R, Koegel C, Bard M: A yeast sterol auxotroph (erg25) is rescued by addition of azole antifungals and reduced levels of heme. Proc Natl Acad Sci U S A, 1997; 14; 94(21): 11173-8.
117. Henry KW, Nickels JT, Edlind TD: Upregulation of ERG genes in Candida species by azoles and other sterol biosynthesis inhibitors. Antimicrob Agents Chemother, 2000; 44(10): 2693- 700.
118. Faucette SR, Wang H, Hamilton GA, Jolley SL, Gilbert D, Lindley C, Yan B, Negishi M, LeCluyse EL: Regulation of CYP2B6 in primary human hepatocytes by prototypical inducers. Drug Metab Dispos, 2004; 32(3): 348-58.
119. Smith CM, Faucette SR, Wang H, LeCluyse EL: Modulation of UDP- glucuronosyltransferase 1A1 in primary human hepatocytes by prototypical inducers. J Biochem Mol Toxicol, 2005; 19(2): 96-108.
120. Svecova L, Vrzal R, Burysek L, Anzenbacherova E, Cerveny L, Grim J, Trejtnar F, Kunes J, Pour M, Staud F, Anzenbacher P, Dvorak Z, Pavek P: Azole antimycotics differentially affect rifampicin-induced pregnane X receptor-mediated CYP3A4 gene expression. Drug Metab Dispos, 2008; 36(2): 339-48.
121. Dring AM, Anderson LE, Qamar S, Stoner MA: Rational quantitative structure-activity relationship

(RQSAR) screen for PXR and CAR isoform-specific nuclear receptor ligands. Chem Biol Interact, 2010; 188(3): 512-25.
122. Kanno Y, Inouye Y: A consecutive three alanine residue insertion mutant of human CAR: a novel CAR ligand screening system in HepG2 cells. J Toxicol Sci, 2010; 35(4): 515-25.
123. Auerbach SS, Ramsden R, Stoner MA, Verlinde C, Hassett C, Omiecinski CJ: Alternatively spliced isoforms of the human constitutive androstane receptor. Nucleic AcidsRes, 2003; 15; 31(12): 3194-207.
124. Zhou S, Lai X: An Update on Clinical Drug Interactions with the Herbal Antidepressant St. Johns wort. Current Drug Metabolism, 2008; 9(5): 394-409.
125. Maladkar M, Tekchandani C, & Dave U: Clindamycin, Clotrimazole and Tinidazole in Mixed Vaginosis-A "Real World" Clinical Experience. Journal of Gynecology and Obstetrics., 2015; 3(3): 49-54.
126. Gupta S, Tripathi R, Singh N, Bhalla P, Ramji S, Mala YM: Pregnancy outcome in asymptomatic women with abnormal vaginal flora without any treatment and after treatment with vaginal clindamycin and clotrimazole: A randomised controlled trial. South African Journal of Obstetrics and Gynaecology, 2013; 19(2): 35-38.
127. Ramchand DB, Shilpa N, Meghana P, Balasaheb G, Pradeep S, Renu B., Efficacy and tolerability of two intravaginal formulations containing clindamycin plus clotrimazole in women with vaginal infections: A pilot study. Pharmacology, Toxicology and Biomedical Reports, 2015; 1(1).
128. Bavya R., Evaluation of common causative oraganisms of abnormal vaginal discharge and effectiveness of short course intravaginal clotrimazole and clindamycin therapy in the same (Doctoral dissertation, Thanjavur Medical College, Thanjavur), 2003.
129. Gaikwad V, Patvekar M, Gupta S, Chaudhari S, Gandham N, Jadhav SV: A study of the role of bacterial vaginosis in preterm labour from tertiary care hospital in India. International Journal of Medical and Clinical Research, 2012; 3(7): 221.
130. Visser LE, Penning-van Beest, FJ, Kasbergen AH, De Smet PA, Vulto AG, Hofman A, Stricker BHC: Overanticoagulation associated with combined use of antifungal agents and coumarin anticoagulants. Clinical Pharmacology & Therapeutics, 2002; 71(6): 496-502.
131. Mignat C: Clinically significant drug interactions with new immunosuppressive agents. Drug safety, 1997; 16(4): 267-278.
132. El-Asmar J, Gonzalez R, Bookout R, Mishra A, Kharfan-Dabaja MA: (2016). Clotrimazole troches induce supratherapeutic blood levels of sirolimus and tacrolimus in an allogeneic hematopoietic cell-transplant recipient resulting in acute kidney injury. Hematology/oncology and stem cell therapy, 2016; 9(4): 157-161.
133. Sam WJ, Chamberlain CE, Lee SJ, Goldstein JA, Hale DA, Mannon RB, Hon, YY: Associations of ABCB1 3435C> T and IL-10-1082G> A polymorphisms with long-term sirolimus dose requirements in renal transplant patients. Transplantation, 2011; 92(12): 1342.
134. Dzintars K, Toman LP: Interpretation and Understanding of Clinical Drug Interactions Between Azoles and Immunosuppressants in Solid Organ Transplant Recipients. Current Fungal Infection Reports, 2020; 1-6.
135. Pejcic, A, Jankovic SM, Opančina V, Babic G, Milosavljevic M: Drug–drug interactions in patients receiving hematopoietic stem cell transplantation. Expert opinion on drug metabolism & toxicology, 2019; 15(1): 49-59.
136. Marian F, Andrea FD, Scott CA, Kelly LC: Immunosuppressants, Psychosomatics, 2004; 45(4): 354-360,
137. Singh SI, Treatment of vulvovaginal candidiasis. Canadian Pharmacists Journal, 2003;136(9)
138. Sherman, R.G. Prusinski, L., Ravenel, M.C. & Joralmon, R.A., Oral candidosis quintessence international, 2004; 33(7).
139. Chiu M: Fungal infections: Understanding. PS Post Script, 2018; 44-47.
140. Patton LL, Bonito AJ, Shugars DA: A systematic review of the effectiveness of antifungal drugs for the prevention and treatment of oropharyngeal candidiasis in HIV-positive patients. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 2001; 92(2): 170-179.
141. Kumar S, Roy V: Amphotericin B Revisited. MAMC J Med Sci, 2021; 7: 104-8.
142. Bachhav YG, Patravale VB: Microemulsion-based vaginal gel of clotrimazole: formulation, in vitro evaluation, and stability studies. AAPS PharmSciTech, 2009; 10(2): 476–481.
143. Umme H, Shivakumar HG, Gowrav MP: Formulation design and evaluation of a novel vaginal delivery system of clotrimazole, International journal of pharmaceutical sciences and research, 2014.
144. Nagoba SN., Purushotham RK, Zakaullah S, Formulation of Clotrimazole as lozenge tablet for improved delivery to ORAL thrush, Journal Of Pharmaceutical And Biomedical Sciences, 2011
145. Whittlesea C, Walker R: Clinical pharmacy and therapeutics. Reprinted 2008, Churchill wingstone publisher, 2007; 4: 599.
146. Tripathi KD: Essential of medical pharmacology. Jaypee brothers medical publishers ltd, 2003; 720: 2.