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"MUCORMYCOSIS – A DISEASE AND ITS TREATMENT WITH COMBINATION OF SYNTHETIC AND INNOVATIVE APPROCH TO HERBAL DRUGS EXTRACT WITH SURGERY"

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ABSTRACT

Mucormycosis is an uncommon but life-threatening infection with nonspecific infection clinical manifestation that makes its diagnosis treatment difficult. Generally from the order Mucorales (Rhizopus, Mucor, Rhizomucor, Absidia, Apophysomyces)cause an Angio invasive infection called an Mucormycosis. Mucormycosis presents with, pulmonary, ,cutaneous, involvement. Mucormycosis has few available treatments including Liposomal Amphotericin B, Amphotericin B Deoxycholate, Itraconazole, Posaconazole or their combination, echinocandin, Voriconazole, and herbal extracts such as Tetradine, Rhizophora mangle, Picrohiza kurrhoa, they are most widely used as antifungal agent.Mucormycosis was difficult to study on imaging study surgery plus antifungal therapy close yields greate rsurvival rate. LAmB is formulation that results in reduce nephrotoxicity as compared with DAmB (Deoxycholate AmphotericinB)while retaining the antifungal effect of active agent. Clinical approach to diagnosis lacks sensitivity and speficity. Development of quantitative Polymerase Chain Reaction(PCR) is promising area of ongoing research to enable more rapid diagnosis. The molecular pharmacology,preclinical,and clinicalpharmacokinetics and clinical experience with LAmB for the most commonly encountered fungal pathogens are reviewed.

Keywords:-

Antifungal agent, mucormycosis liposomal Amphotericin B, surgery, herbal extract,Amphotericin B Deoxycholate.

INTRODUCTION

Mucormycosis are lifethreating Invasive Fungal Disease(IFD) .Pulmonary or disseminated disease are commonly found in immunosuppressed patient (hematological malignancy , hematopoietic stem cell transplantation) , rhino-orbito-cerebral form in diabetic patients, cutaneous forms in patient having trauma, other localization (GIT, endocarditis, isolated cerebral infection) are less frequent. Resent re classification has abolished the order Zygomycetes and placed the order Mucorales in the sub phylum mucormycotina. Therefore, we refer to infection caused by Mucoralesas mucormycosis rather than Zygomycosis.

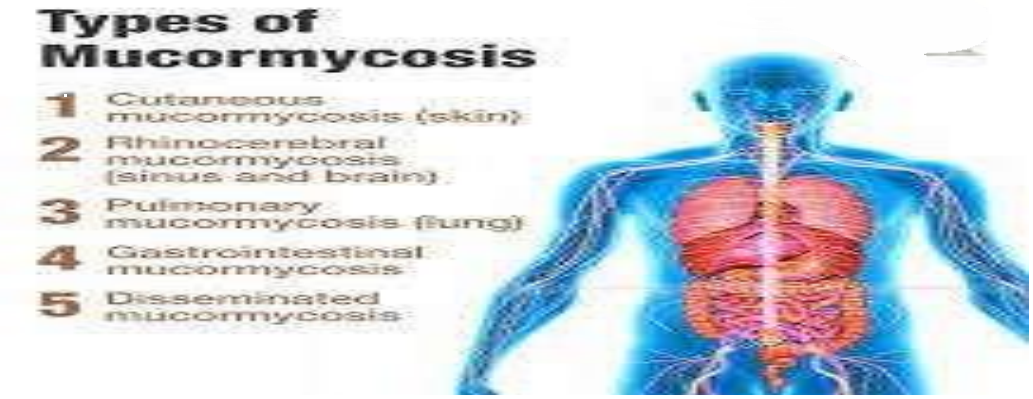

Fig.1 Types of mucormycosis

Risk factors: Most of the patients proneto mucormycosis have weakened immune system and other underlying medical condition. The Risk factors mainly include:

- Diabetes mellitus, especially with diabetic keto acidosis
- Cancer
- Longterm corticosteroid use and Organtransplant
- HIV/AIDS

Mucormycosis are developed on skin after fungus attack through a cut, scrape ,burn or any other trauma.Mucormycosis fungal infection which leads to causes increasing mortality. Among the mucoraceae, Rhizopusoryzae (Rhizopusarrhizus) was more common cause of infection.

Here,we review treatment with combination of synthetic and herbal drugs, also by surgery.

❖ **Synthetic antifungal agent for mucormycosis treatment is such as:-**

1. Polyenes: - Liposomal amphotericin B (LAmB) ,Amphotericin B deoxycholate(AMB)
2. Azoles: - Intraconazole, Voriconazole, Posaconazole

❖ **Combination antifungal therapy for mucormycosis**

a) Echinocandins
b) Importance of surgery in mucormycosis

❖ **Herbalextract**-Tetradine ,Rhizophoramangle ,Picrohiza kurrhoa, Catharanthusroseus, lanatacamara, Sida cordifolia, Carvacrol, Thymol, Curcumin, Piperin

EARLY DIAGNOSIS OF MUCORMYCOSIS

Initially the polyenes therapy within 5 days after diagnosis of mucormycosis was associated with improvement in survival. Therefore, establishing an early diagnosis of mucormycosis is critical to enable early initiation of active antifungal therapy.

Progress has been made in improving laboratory yield of cultures for mucormycosis, the development of other diagnostic methods is major unmet need for this infection.

Development of quantitative Polymerase Chain Reaction (PCR) system is a promising area of ongoing research to enable more rapid diagnosis. For example, Kasai et al developed 2real time quantitative polymerase chain reaction assays that targeted the 28SrRNA gene for diagnosis of mucormycosis caused by

Rhizopus, Mucor and Cunnighamella species. Thepolymerase chain reaction assays successfully detected circulating DNA in rabbits with experimental pulmonary mucormycosis.

In Rhino-orbital cerebral disease, Computed Tomography (CT scan) typically reveals only sinusitis, so computed tomography that indicates the absence of deeper infection does not rule out mucormycosis.

Magnetic Resonance Imaging (MRI) is more sensitive than CT scan for detecting orbital and CNS involvement.

CT is useful for early detection of pulmonary mucormycosis, particularly in patient with cancer. further refinement of radiographic techniques for distinguishing mucormycosis from other infectious and non-infectious disease is an important area for future research.

PATHOPHYSIOLOGY

The phagocytes as primary host defence against mucormycosis ,hence these causes' chance of infection of mucormycosis in persons who has low number of phagocytes.

Normal immune cells such as mononuclear and polymer phon uclear phagocytes take up and
Kill hyphae and spore of molds by generation of oxidative metabolite , cationic peptide
Defense in and neutron peniais main cause of mucormycosis

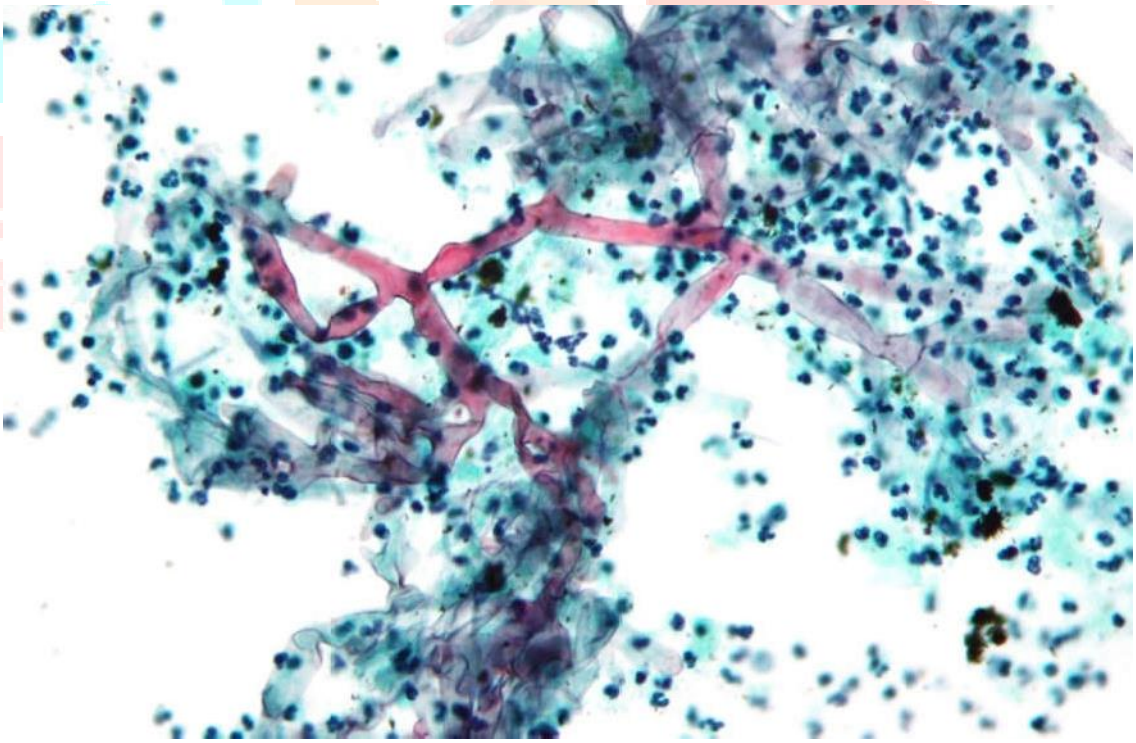

Fig.2:Pathophysiology of Mucormycosis

If serum is acidified to pH Rhizopus can grow fastly, because acidic pH dissociates iron protein complex and make free iron available for fungal cell. Chelation not the mechanismby which deferoxamine enables the Mucormycosis infection. Iron chelators significantlydecreased thegrowth of Rhizopus, other function siderophores actually deliver iron tofungal cell and promote growth, patients taking deferoxamine for iron overload related tohemodialysis have significant chance of infection, deferoxamine is a siderophore

producednaturally bacteria and function as a xenosiderophore to deliver iron to Rhizopus growing invitro. Deferoxamine has high affinity for iron and can extract iron from transferrin andferritin. Rhizopus and deferoxamine made a deferoxamine iron complex and reduces ferrictoferrous iron during intracellular transport. Rhizopus genome contain side rophore, Mucorales have multiple mechanism to acquire scarce but essential iron ions from an environment that does not easily give the mup.

Mucorales virulence factor that have link to pathogenesis. Mucormycosis has specialty forattack on endothelial cell of vascular system and capability to spread disease from primary site of infection .Rhizopus binds to macromolecules of the extracellular matrix culture.

ANTIFUNGAL THERAPY

Synthetic antifungal agent:-

To treat Mucormycosis is difficult for clinician because there is a problem for clinician to choose medicines for clinical trials. Animal models are developed to study infection in vivo include intravenous, intranasal and intrasinus in mice model. Species used in these model R.oryzae ,R.microspore , Mucor, Absidiaspp .Due to lack of clinical trials for mucormycosis -there are different antifungal strategies are evaluated.

1. Polyenes:-

Amphotericin B deoxycholate from 50 years used as an antifungal agent bactericidal resistance saw in isolated Liposomal Amphotericin B less toxic than Amphotericin. In clinical study, high dose of Amphotericin B in animal model superior. Amphotericin B lipid complex inferior to CNS penetration vs Liposomal Amphotericin B in one rabbit study not superior for placebo Amphotericin B at a high dose.

However, lipid formulation of Amphotericin B is less nephrotoxic and can be administered safely at higher doses for longer period of timethan Amphotericin B.

In salvage therapy for mucormycosis Amphotericin B lipid complex (ABLC) resulted in71%successrate.

And treatment with Liposomal Amphotericin B (LAmB)was associated with 67% survival rate and compared with (AmB)was with 39% survival among patient with cancer who experienced mucormycosis. Thus, lipid formulation of Amphotericin B appears to be safer,effective, alternative to AmB to treat mucormycosis. Liposomal Amphotericin B (LAmB)over Amphotericin B Lipid Complex (ABLC) for treating Central Nervous System (CNS) Mucormycosis.

- **Molecular Pharmacology of Liposomal Amphotericin B (Lamb)**

Liposomes are spherical vesicles inne rcore is characterized by aqueous core and surrounded by lipid bilayer. Liposomes can been gineered to maximize antifungal activity

And minimize drug related toxicity. LAmB was designed to enable parenteral administration in Liposomes,because the stability will be increased in Liposomal Amphotericin B.

The lipid structure of LamB has 3 major components–

I. Hydrogenated soy phosphatidylcholine
II. Distearoyl phosphatidyl glycerol
III. Cholesterol

The Liposomal Amphotericin B is more effective than the Amphotericin B deoxy cholate having doubling survival rate in R. oryzae infection in ketoacidosis of mice. Study had performed on rabbit Liposomal Amphotericin B penetrated brain parenchyma at level morethan five times of Amphotericin B lipid

complex.in opposite to LAmB and ABLC did not improve survival rate when compared with Amphotericin B deoxycholate in murine model of R.oryzae infection.

Recently in clinical mucormycosis,theLiposomal Amphotericin B is effective.From animal data. Pharmacokinetic studied, retrospective clinical data for first line use of highdose Liposomal Amphotericin B for mucormycosis and other hand Amphotericin B lipid complex used for CNS disease as an alternative anti fungal agent.

Therefore, the Liposomal Amphotericin B at dose 10mg/kg/day is very useful in case of lifethreatening mucormycosis injection and immediate action.

- **Mechanism of action:-**

Amphotericin B is binding to ergosterol in the fungal cell membrane, which forms pores on

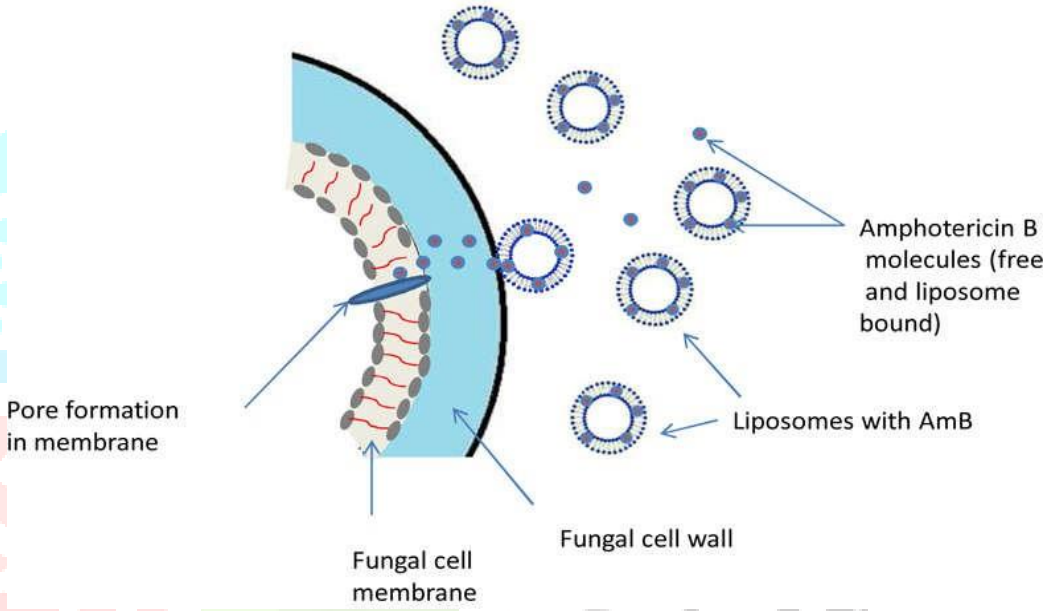

Fig 3. Mechanism of Liposomal Amphotericin B

the cell and that causes ion leakage and ultimately cell death.

The Amphotericin B and empty Liposomes both loaded with binding of liposomes to the cell wall of pathogenic yeast and molds by using fluorescently labeled liposomes and gold-label liposomeshas been demonstrated in-vitro and in-vivo.

Liposomes without AmB bind to fungal cell wall, but both 'empty' liposomes and fungal cell remain intact. The binding of Amphotericin B containing liposomes results in fungal cell death and binding results in liposomal disruption and release of Amphotericin B, by binding to ergosterol in fungal cell membrane will gives fungicidal activity.

Azoles:-

In previous study, Itraconazole is used as antifungal agent against Rhizopus and Mucorspecies susceptible in-vitro. Drugs did not show activity in-vivo against hyper susceptible strain of Absidia that's

why Itraconazole were not consider first line agent but it considered as adjuctive therapy.

Voriconazole is a broad spectrum triazole, but not active against Mucorales in-vitro. In mucormycosis treatment, there are some investigational triazole have mainly effective

in-vitro. The Posaconazole is superior than Itraconazole in animal model but less efficacious than Amphotericin B deoxycholate.

The Posaconazole therapy is effective for refractory mucormycosis. The patients who do not respond to Amphotericin therapy in rhinocerebral disease with Amphotericin Bandheart/kidney transplant patient the azoles are successfully used in treatment.

Furthermore, data from murine models of mucormycosis (in which serum Posaconazole levels are>5µg/mL)raise further concern sab out the efficacy of Posaconazole for mucormycosis. In neutropenic mice infected with Mucor species. found that Posaconazole was statistically significantly less effective than was AmB. found that Posaconazole was less effective than AmB in treating mice infected with Rhizopus microspores or Absidiaspecies.In addition, they found that Posaconazole was no better than placebo for treating R.oryzae, which causes >70% of clinical cases of mucormycosis. Finally, in 2 more-recent studies, Posaconazole mono therapy was also no better than placebo for the treatment of R.oryzae infection in neutropenic or DKA mice. Thus, data from 4 groups of investigators indicated that Posaconazole was inferior in efficacy to AmB for the treatment of murine mucormycosis, and 3 groups found that it was not superior to placebo for treating mice infected with R. oryzae.

Combination antifungal therapy for Mucormycosis:

Echinocandins:-

In evaluation in-vitro, capsofungin was used as antifungal drug having less activity against agent of mucormycosis.

In-vitro capsofungin activity against mold remain unclear. In research, it was found that Amphotericin B Lipid Complex (ABLC) and caps of ungin plus was shown synergist action. The study suggests that echinocandins consider as second agent. The combination improves survival rate by 50%.In a recent, small ,retrospective study ,combination LFAB-capsofungin therapy was associated with significantly improved outcomes for rhino-orbital cerebral mucormycosis among patients with diabetes, compared with polyene monotherapy. By multi variate analysis,only combination therapy was significantly associated with superior outcomes. We emphasize that these data require confirmation in a prospective,randomized trial. In the mean time , if combination LFAB-echinocandin therapy is considered for mucormycosis, echinocandins should be administered at US Food and Drug Administration approved dosages.Increasing the dosage of the echinocandins is not advisable because of a para doxical loss of efficacy against murine mucormycosis at dosages >3mg/kg/day.

- **Importance of Surgery in Mucormycosis:-**

Antifungal therapy in mucormycosis treatment use to control the infection. Mucormycosis having a susceptibility to antifungal agents, strain may be highly resistant to AmphotericinB ,angio invasion ,thrombosis result in poor penetration of anti-infective agent to the infection.

Antifungal agent may be ineffective in-vivo but causative organism was susceptible to the therapy in-vitro.

Surgery is need for tissue necrosis occurred in mucormycosis which not be prevented by killing the organism. On urgent therapy the surgical debridement of the infected tissue to be performed. Repeated detection of sinuses and orbit may need to ensure that necrotic tissue had been decided and infection have been progressed.

On the basis of previous studies there are 65% patients with Rhinocerebral , cutaneous (skin),pulmonary (lungs) mucormycosis cured with surgery.

Blood vessels thrombosis and resulting necrosis during mucormycosis can result in poor penetration of antifungal agent to the site of infection. Therefore, debridement of necrotic tissues may be critical for complete eradication of mucormycosis. In logistic regression model, surgery was found to be an independent variable for favorable outcome among patients with mucormycosis. From this data support the concept that surgical debridement is necessary to optimize cure rate.

Innovative approach to herbal drug extract in Mucormycosis treatment:

Medicinal plant is having great importance to health of individual and communities, and their importance lies in chemical substance that produce a definite physiological action on body. Herbal remedies tend to have more complex and mix of chemicals and can sometimes offer access to drug or combination of drugs. These natural compounds formed the basis of discovering modern drugs. Some of the antifungal drugs most recently introduced in clinical practice are echinocandins and sordarines derived from natural products. Herbal formulational ways has attracted considerable attention due to their good activities and comparatively lesser side effects when compared to synthetic drugs.

Pharmaceutical composition comprising tetrandrine and one or more azole antifungal drugs (voriconazole,fluconazole)for treating fungal infection (candidiasis,mucormycosis). Tetradine is an iso quinoline alkaloid isolated from roots of Stephaniatetrandra .Tetradine inhibits fungi's mycelial phase (candida albicans) in a concentration dependent manner ,reverse fungi's resistance to azole drugs ,and improve fungi's sensitivity to azole medicines. For example, ointment comprising tetrandrine (1% w/w) and fluconazole (1% w/w) in petroleum jelly, capsule composition comprising tetrandrine and fluconazole (1:10 to 1:20ratio)in medicinal glucose powder.

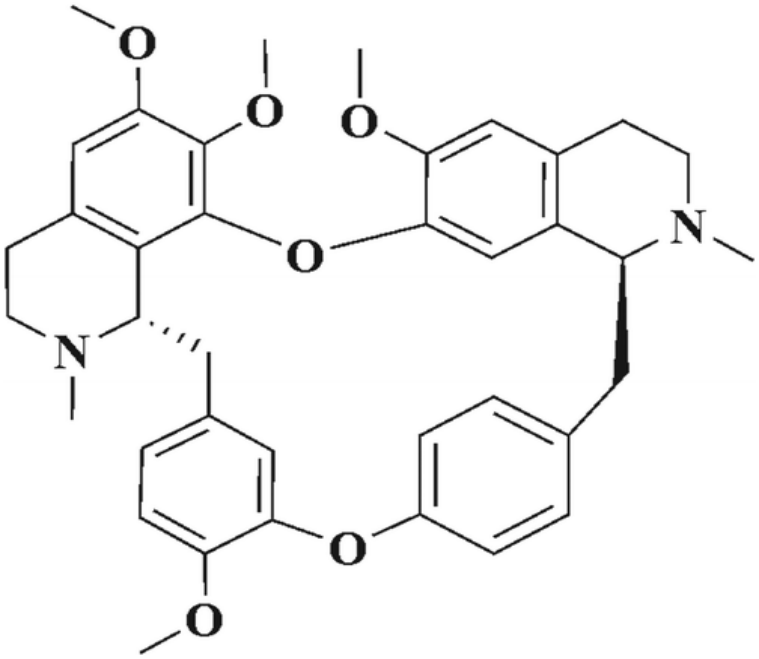

Fig. Structure of Tetradine 4.

The composition containing one or more terpenes (steroidal tri terpenes, steroidal tri terpen ester, steroidal tri terpen ester fatty acids) and one or more fatty acids (long chain fatty acids) collected during an on-aqueous extraction(n hexane ,pentane ,ethyl acetate ,ether ,chloroform) of the roots/rhizome of Neopic rorhiza Scrophularii flora and Picrohiza Scrophularii flora.

The palatable composition comprises more than 50% by weigh tof the lipophilic components (terpenes and fattyacids).

The anti-infective extract of different parts (cortices, bark, flower, seeds, roots, rhizome orstems) of Rhizophora mangle, which can block the reproductive capabilities of microbes(fungi virus, bacteria)and tumors.

The hot water decoction extracts were obtained after drying whole plant or its parts. This applications state that extracts contain anti-infective compounds. However, no chemical compound has been suggested along with its structure in this application. The extract can be taken orally or applied directly to the skin as disinfectant hand gel to fight microbial

Infection (mucormycosis). This application exemplifies a clinical case study to treat a common viral cold.

A medicinal, nutraceutical or food composition in the form of tablet or capsule forelimination treatment or management of infection (mucormycosis)in human in need there of consisting essentially of therapeutically effective amount of hexane and liquid carbon dioxide extract of roots and rhizome of Picrorhiza Kurrhoa. The previous study employed the solid plant material was extracted with hexane and liquid carbon dioxide. These extracts are supposed to contain lipophilic constituent(terpenes) of medicinal value.

A method for treating a microbial infection (Mucormycosis)comprising administering to a subject in need there of an aminoglycoside and at least one compound selected from the group consisting of Carvacrol (Origanum vulgare), Thymol (Thymus vulgaris), Curcumin(Curcumalonga) antipurine(Pipernigrum).

It has been shown that these combinations have synergistic antimicrobial activity against logphase (i.e.,Multiplying) and clinically latent microorganism which offers the short en chemotherapy regimen and reduce the emergence of microbial resistance associated with use of such combinations.

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The in vitro antimycotic activity of leaf extract of Catharanthus roseus, Nerium indicum,Sida cord ifolia was studied against M.circinelloides. This fungal species causes mucormycosis (black fungus). This study supports the traditional medicinal use of various plant extract (Catharanthus roseus, Lanata camara, Nerium indicum, Sida cordifolia) in treating infectious disease,at present of those people suffering from mucormycosis.

Myrtaceae	**(Guava)Psidiumguajava**
	(Neem)Azidarachtaindica
	Meliaceae
Fabaceae	**Zingiberaceae**
Zingiberaceae	**Turmeric(CurcumalongaL.)**
Myrtaceae	**(Cherry)Eugeniauniflora**
Mimosaceae	**Mimosatenuiflora**
Solanaceae	**(Brinjal)Solanummelongena**
Euphorbiaceae	**(IndianCopperleaf)Acalyphaindica**
Menispermaceae	**Guduchi(Amruthballi)Tinosporacordifolia**
Apiaceae	**Indianpennywort(Gotukola)Centellaasiatica**
Amaranthaceae	**MountainKnotGrass(GorakhbutiorChhaya) Aervalanata**
Verbenaceae	**(IndianprivetorWild.Jasmine)Clerodendrumin erme**

Fig.5.Medicinal Plants With Antifungal Activity

CONCLUSION:

Mucormycosis treatment recommendation were recently updated by the ECCM. LAmB is the first line drug in mucormycosis therapy and LAmB formulation reduces nephro toxicity as compared to DAmB. Itraconazole and Posaconazole formulation have been added in second line treatment for mucormycosis. Echinocandins are also second line treatment with combination of Amphotericin B lipid complex and Capsofungin plus was shown synergistic action.Herbal extract such as Tetradine ,Rhizophoramangle ,Picrohizakurrhae ,Catharanthus roseus, lanata camara, Sida cordifolia they are most widely used as antifungal agent. Mucormycosis was difficult to study on imaging study hence surgery plus antifungal therapy close yield greater survival rate. They are particularly complex to implement in context of low incidence disease.Few advances have been made on mucormycosis treatment.

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