

**CONCEPTUAL UNDERSTANDING ON ANTIFUNGAL ACTIVITIES OF AYURVEDIC PLANTS ON RHINO-ORBITO-CEREBRAL MUCORMYCOSIS****Vd. Mahejabeen M. Jikare<sup>\*1</sup>, Dr. Prof. Nilakshi S Pradhan<sup>2</sup> and Dr. Prof. Sharayu Kore<sup>3</sup>**<sup>1</sup>M.S (Scholar), Dept. of Shalakyatantra, Sumatibhai Shah Ayurved Mahavidyalaya, Hadapsar, Pune.<sup>2</sup>Professor, Ph.D. (Ayu)(Shalakya Tantra), M.S.(Ayu)(Shalakya Tantra), Sumatibhai Shah Ayurved Mahavidyalaya, Hadapsar, Pune.<sup>3</sup>Professor, H.O.D. Dravyaguna Vigyana, Sumatibhai Shah Ayurved Mahavidyalaya, Hadapsar, Pune.**\*Corresponding Author: Vd. Mahejabeen M. Jikare**

M.S (Scholar), Dept. of Shalakyatantra, Sumatibhai Shah Ayurved Mahavidyalaya, Hadapsar, Pune.

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**ABSTRACT**

Mucormycosis represents a group of life-threatening infections caused by fungi of the order mucorales. It is severe and rare fungal illness, mucormycosis also called 'Black fungus', It affects some corona virus patients. It is more severe in people with comorbid conditions like Diabetes and immune compromised state. Aggressive treatment used for management of mucormycosis after diagnosis of this disease, though its mortality rate is more. The treatment cost is also very high and needs a long course of treatment. There are cost effective, potent and broad-spectrum antifungal agents are described in Ayurveda. This current article describes conceptual understanding on antifungal activities of Ayurvedic plants on Rhino-orbito-cerebral mucormycosis. The most common type of mucormycosis is rhino-orbito-cerebral mucormycosis.

**KEYWORDS:** Mucormycosis, Antifungal activity, COVID 19, Ayurveda.**INTRODUCTION**

The pandemic coronavirus disease 2019 (COVID-19) produces significant problem worldwide. Several treatment options have been tried none is useful only systemic glucocorticoids show improvement in survival rate of covid 19 patients<sup>[1]</sup> Mucormycosis are more severe with comorbid conditions like Diabetes and immune compromised state. Many states have declared Mucormycosis infection as an epidemic because of increase in number of mucormycosis patients and has become a matter of huge concern.<sup>[2]</sup>

Fungi of the order Mucorales belong to six families, all of which can cause mucormycosis. Rhizops oryzae (in the family mucoraceae) is by far the most common cause of infection. Mucormycosis can be divided into at least six clinical categories based on clinical presentation and involvement of a particular anatomic site, rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated and miscellaneous.<sup>[3]</sup>

The clinical features described of Rhino-orbito-cerebral mucormycosis are similar to Raktaja Pratishyaya (Vitiated Rakta, occupying nasal Sira precipitate Raktaj Pratishyaya. It is characterized by blood stained discharge from nose, emitting foul smell from nose and mouth along with crawling and expelling white, unctuous, small worms/maggots through nose, itching in ear, eyes, nose; anosmia; coppery red eyes, Uroghata

with suptata i.e. features due to chest injury with loss of sensation in chest etc.)<sup>[29]</sup> and Krimija Shiroroga (unilateral facial swelling, Headaches, Nasal congestion, Nasal discharge, Fever etc and Features of Pittaja Shiroroga along with a characteristic feature of hyperesthesia /intolerance to touch). Presentation of Pulmonary mucormycosis are very much similar to Kshayaja Kasa, (Cough with pericardial chest pain, foul smelling, greenish, purulent, mucoid and blood stained/ haemoptysis sputum and cough associated with fever (Jvaro-mishrakriti) or chest pain (Parshvaruka) or recurrent coryza (Pinasa) are the clinical features found in Pulmonary Mucormycosis. The Gastrointestinal Mucormycosis can be included under the spectrum of Udara roga especially Sannipatika udara roga and pathogenesis of Disseminated mucormycosis in later phase can be compared with Dushtavrana whereas Cutaneous mucormycosis can be correlated with Kushtha (Loss of sensation of touch, excess or less perspiration, discoloration of skin, formation of various types of pustules and pidika, itching, pain lethargy and weakness)<sup>[30]</sup> and Visarpa. (Skin becomes red hot, swollen and hard, raised skin margin, pustules, ulcers, fever, thirst, vertigo and diarrhea).<sup>[31]</sup>

There are three stages of classical clinical progression of Rhino-orbito-cerebral mucormycosis<sup>[32]</sup>

Stage I: Infection of the nasal mucosa and sinuses.

Stage II: Orbital involvement (orbital apex syndrome,

superior orbital fissure syndrome).

Stage III: Cerebral involvement in which intracranial spread occurs via one of the following routes:

1. Ophthalmic artery.
2. Superior orbital fissure. Spreading via this route may cause sinus thrombosis and internal carotid artery thrombotic occlusion.
3. Cribriform plate. The spread of the infection to the frontal lobes and to the cavernous sinus occurs via perivascular and perineural channels through the cribriform plate and the orbital apex, respectively

The best ways to avoid Mucormycosis infection are early detection of infection, boosting immune system of patients and break the cycle of infection. The Ayurvedic principle of management consist of Krimihara, Kledahara, Pramehahara, Agnivardhaka, Aampachaka, Ojovardhaka, Rasayan and Balya chikits.<sup>[2]</sup>

The most common type of mucormycosis is rhino-orbito-cerebral mucormycosis.

Amphotericin-B is commonly used for the treatment of this infection and the cost of this treatment is expensive due to use of high cost anti-fungal medicines, prolonged hospital stays etc. because of the complications include severe damage to the involved organs, it needs costly procedures for proper management. As allopathic medicines system involves high cost health approach and it is not affordable for common patients. Ayurveda consist of cost effective, potent and broad spectrum Anti-fungal agents which need to be included in the treatment protocol of mucormycosis.<sup>[1]</sup>

**AIM:** To review antifungal activity of few Ayurvedic plants on Rhino-orbito-cerebral mucormycosis

## OBJECTIVES

- 1) To study the concept of mucormycosis
- 2) To find out potential drug which can be used for repurposing the drug in Rhino-orbito-cerebral mucormycosis.

## METHODS AND MATERIALS

Ayurvedic Samhitas and modern textbook were screened for mucormycosis disease and also online search was done by keywords mucormycosis in COVID 19 and Antifungal Ayurvedic plants.

### Disease review

**Etiology** - Fungi of the order Mucorales belong to six families, all of which cause mucormycosis. These are *Rhizopus oryzae*, *Rhizopus microspores pusillus*, *mycocladus corymbifer*, *Apophysomyces elegans* and *Mucor* species.<sup>[3]</sup>

**Pathogenesis-** The Mucorales are ubiquitous environmental fungi to which humans are constantly exposed. These fungi cause infection primarily in patients with diabetes or defects in phagocytic function

(e.g. associated with neutropenia or glucocorticoid treatment). Patients with elevated level of free iron, which supports fungal growth in serum and tissues. In iron overloaded patients with end stage renal failure, treatment with deferoxamine predisposes to the development of rapidly fatal disseminated mucormycosis; this agent, an iron chelator for the human host, serves as a fungal siderophore, directly delivering iron to the Mucorales.

Furthermore, patients with diabetic ketoacidosis (DKA) are at high risk of developing rhinocerebral mucormycosis, the acidosis causes dissociation of iron from sequestering proteins likely that hyperglycaemia during DKA also contributes to the risk of mucormycosis through its association with poorly characterized defects in phagocytic function.<sup>[3]</sup>

### Epidemiology

Mucormycosis typically occurs in patients with diabetes mellitus, solid organ or hematopoietic stem cell transplantation (HSCT), prolonged neutropenia or malignancy. Patients using antifungal prophylaxis with either itraconazole or voriconazole may be at increased risk of mucormycosis.<sup>[3]</sup>

### Clinical manifestation<sup>[3]</sup>

Mucormycosis can be divided into at least six clinical categories based on clinical presentation and involvement of a particular anatomic site, rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated and miscellaneous.

Rhinocerebral mucormycosis continues to be the most common form. Most cases occur in patients with diabetes, Glucocorticoid etc. Symptoms are nonspecific and include eye and facial pain and facial numbness, conjunctival suffusion, blurry vision and soft tissue swelling. fever may be absent up to half of cases, while white blood cell counts are typically elevated as long as the patient has functioning bone marrow. If untreated, infection usually spreads from the ethmoid sinus to orbit, resulting in compromise of extraocular muscle function and proptosis, chemosis, vision loss, ophthalmoplegia and suggests the development of cavernous sinus thrombosis.

Upon visual inspection, infected tissue may appear to be normal during the earliest stage of fungal spread and then progress through an erythematous phase, with or without edema, before the onset of a violaceous appearance and finally development of a black necrotic eschar. Infection can sometimes extend from the sinuses into mouth and produce painful necrotic ulcerations of hard palate, but this is a late finding that suggest extensive well-established infection.

Pulmonary is second most common manifestation. Symptoms include dyspnoea, cough, chest pain, fever.

Angioinvasion results in necrosis, cavitation, haemoptysis'

Cutaneous mucormycosis may results from external implantation of the fungus or hematogenous. It is highly invasive penetrate into muscle, fascia and even bone causing necrotizing fasciitis.

Gastrointestinal mucormycosis has occurred in premature neonates in association with disseminated disease and necrotizing enterocolitis.

Hematogenously disseminated mucormycosis may originate from any primary site of infection. Most common site is brain, but metastatic lesions may also be found in any other organ.

Biopsy with histopathological examination, CT (Computerized Tomography) or MRI (Magnetic resonance imaging) of the head or sinuses

#### Differential diagnosis

Other mold infections, including aspergillosis, scedosporiosis, fusariosis, dematiaceous fungi

#### Treatment

- 1) Early diagnosis
- 2) Reversal of underlying predisposing risk factors, if possible
- 3) Surgical debridement
- 4) Prompt antifungal therapy

#### Diagnosis

#### Medicinal plants having antifungal activity

Table no. 1: Rasapanchaka (Ayurvedic pharmacodynamics).<sup>[4]</sup>

Drug	Family	Rasa	Virya	Vipaka	Effect on Dosha	Guna	Karma
Sunthi <sup>[4]</sup> ( <i>Zingiber officinale</i> Roxb.)	Zingiberaceae	Katu	Ushna	Madhura	Vatashamak, Kaphashamak	Laghu, Snigdha	Amapachana, kasa, Shvasa
Nimba <sup>[5]</sup> ( <i>Azadiracta indica</i> )	Meliaceae	Tikta, Katu, Kashaya	Sheeta	Katu	Pitta-Kaphashamaka	Laghu, Ruksha	Krimi, Kushtha
Ashvagandha <sup>[6]</sup> ( <i>Withania somnifera</i> Linn.Dunal)	Solanaceae	Madhur, Tikta, Kashaya	Ushna	Madhur	Vata-Kaphashamak	Laghu, Snigdha	Shvitra, Kushtha, Kshayapaha
Haridra <sup>[7]</sup> ( <i>Curcuma longa</i> Linn.)	Zinziberaceae	Tikta, Madhur	Ushna	Katu	Pitta-Kaphashamak	Laghu, Ruksha	Tvagadosha-Shotha-vranapaha, Kushthaghni
Kantakari <sup>[8]</sup> ( <i>Solanum Xanthocarpum</i> . Burm.)	Solanaceae	Tikta, Katu	Ushna	Katu	Vata-Kaphashamak	Laghu, Ruksha, Sara	Krimighna, Shvasa, Kasa
Kumari <sup>[9]</sup> ( <i>Aloes vera</i> . Tourn ex Linn)	Liliaceae	Tikta, Madhur	Ushna	Katu	Tridoshashamaka	Laghu, Ruksha	Kushtha, Shotha, Kamala, Dipan, Pachana
Rason <sup>[10]</sup> ( <i>Allium sativum</i> )	Liliaceae	Katu, Madhur, Lavana, Tikta, Kashay	Ushna	Katu	Vata-Kaphaghna	Snigdha, Tikshna	Aamapachan, Balya, Rasayan
Tulasi <sup>[11]</sup> ( <i>Ocimum sanctum</i> . Linn)	Labiatae	Katu, Tikta	Ushna	Katu	Tridoshashamaka	Laghu, Snigdha, Tiksha	Jantughna, Kushtha, Shvasa, Kasa
Vacha <sup>[12]</sup> ( <i>Acorus calamus</i> Linn)	Araceae	Tikta, katu	Ushna	Katu	Vata-Kaphashamak	Laghu, Tikshna, Ruksha	Jvara, kandhya, krimighna, Medhya
Vasa <sup>[13]</sup> ( <i>Adhatoda vasica</i> . Nees)	Acanthaceae	Tikta, Kashay	Sheeta	Katu	Pitta-Kaphashamak	Laghu, Ruksha	Jantughna, Kushtha, Kshaya, Shvasa, Kasa
Yashtimadhu <sup>[14]</sup> ( <i>Glycyrrhiza glabra</i> . Linn)	Leguminosae	Madhur	Sheeta	Madhur	Vata-Pittashamaka	Guru, Snigdha	Vranashotha, Shvasa, kasa, Urakshata
Nagavlli ( <i>Piper betle</i> Linn) <sup>[15]</sup>	Piperaceae	Kashay, Tikta, Katu	Ushna	Katu	Vatashamaka	Tikshna, Laghu, Vishada, Sara	Balya, Shleshmahra,

**Actions and Uses**

1. Sunthi- Amavata (Rheumatoid arthritis), Digestion(pachani), aphrodisiac, improves voice, cure vomiting, dyspnoea, spasmodic pain, gastric, heart diseases, filariasis(shlipada), oedema, haemorrhoids, flatus, Grahi(absorbent), Bhedana(Which break the hard faecal matter)<sup>[4]</sup>
2. Nimba- leaves are beneficial for eyes, acts as vermifuge(krimi), diminish pitta and poisonous effect, use in all type of distaste, skin disease(kushtha), appetizer (Agni)<sup>[5]</sup>
3. Ashvagandha- Balya(acts as tonic), Rasayani(tissue vitalizer), atishukral(increases quality of semenshitra(vitiligo), Shotha(oedema), kashaya(wasting)<sup>[6]</sup>
4. Haridra- Krimighna (skin disease), varnya, Glycosuria, Rakta disease, oedema, anaemia, heals wounds.<sup>[7]</sup>
5. Kantakari- laxative, appetizer(dipani), laghu (light in action), digestant (Pachani), diminishing cough, dyspnoea, fever, shukral (semen quality), worm manifestation (Krimi), cardiac problems, kandu(itching), fever<sup>[8]</sup>
6. Kumari- Bhedini (expels out hard faeces), Netrya (good for vision), Rasayani(nourishing), Balya (acts as a tonic), Vrushya(aphrodisiac), Cures intestinal growth, spleen and liver problem, burns, pitta-Rakta and skin diseases<sup>9</sup>
7. Rason – Tissue vitalizer (Brihana), aphrodisiac, digestive(pachana), laxative(sara), heals fracture, good for voice, Bala(tonic), Medhya (brain tonic), netrya(good for eyes), Rasayan, fever, abdominal pain, skin disease(kushtha), dyspnoea, Kapha disease<sup>[10]</sup>
8. Tulasi- appetizer (dipani), Rakta and Skin disease (Kushtha), dysuria<sup>[11]</sup>
9. Vacha- emetic(vanti), appetizer(vanhikrita), vibandha (abdominal distention), spasm, laxative, mild diuretic, apasmar(epilepsy), unmad(insanity), worm infestations<sup>[12]</sup>
10. Vasa- Kushtha(skin disease), meha(diabetes), cough, dyspnoea, fever, vomiting, kshaya(wasting), Rakta diseases<sup>[13]</sup>
11. Yashtimadhu- Chakshushya (good for eyes), Bala(strength), Varna (promotes complexion),shukral(semen quality increases), hair tonic(keshya), improves voice, vrana(inflammatory oedema, poisonous effects, vomiting, thirst, tiresomeness, wasting<sup>[14]</sup>
12. Nagavalli- Balya(strength), mild laxative, ksara property, light in action, may aggravate bleeding tendency, removes kapha and bad odour from oral cavity clears the tartar(mala)<sup>[15]</sup>

**Samprapti Bhanga**

Sundhi, Nimb, Ashvagandha, Haridra, kantakari, Kumari, Rason, Tulasi, Vacha, Vasa, Yashtimadhu, Nagavalli all these are powerful herb described in Ayurveda. These plants show Kledahara, Pramehahara, Agnivardhaka, Aampachaka, Krimihara,

Ojovardhaka, Rasayan and Balya properties which is useful for the treatment of Mucormycosis.<sup>[2]</sup>

**Chemical composition of medicinal plants having Antifungal activity<sup>[16]</sup>****Zingiber officinalis<sup>[17]</sup>:**

Ginger contains the compound caprylic acid.

**Azadirachta Indica<sup>[18]</sup>:**

6-deacetylnimbin, azadiradione, nimbin, salannin and epoxyazadiradione. Pure azadiradione, nimbin, salannin and epoxy-azadiradione did not have appreciable activity. However, when these terpenoids were mixed and bioassayed, they showed antifungal activity.

**Withania somnifera<sup>[19]</sup>**

Withanolides, Withanone, S. Withasomidienone and alkaloids cuscohygrine, 3 tropylogloate.

**Curcuma longa<sup>[20]</sup>**

Turmeric oil and curcumin, isolated from Curcuma longa L., were studied against fifteen isolates of dermatophytes.

**Solanum xanthocarpum<sup>[21]</sup>**

Methanolic extract, Steroidal alkaloids, Solasodin, Solamargine and sterols like cycloartenol nor-carpestrol

**Aloe vera<sup>[22]</sup>**

Aloin, aloe emodin, chrysophenol, chromone derivatives

**Allium sativum<sup>[23]</sup>**

Ajoene, allinase, volatile compounds like allyl alcohol, allyl thiol

**Ocimum sanctum<sup>[24]</sup>**

Eugenol, beta caryophyllene, bornyl acetate beta elemene, nerol

**Acorus calamus<sup>[25]</sup>**

Asarone, palmitic heptilic, butyric acids, calamol, sesquiterpene ketones, alcohols, hydrocarbones

**Adhatoda vasica<sup>[26]</sup>**

Alkaloids and essential oil

**Glycyrrhiza glabra<sup>[27]</sup>**

Licorice, Glycyrrhizine, Glabrenin A&B, Glabrone

**Piper betel<sup>[28]</sup>**

Ethanol extract, Essential oil, Amino acids, Vitamins and enzymes

**DISCUSSION**

Mucormycosis is a severe fungal infection caused by mucorals belong to six families. It is divided into six clinical categories, out of which Rhinocerebral mucormycosis is the most common form. The clinical features described of Rhino-orbito-cerebral mucormycosis are similar to Raktaja Pratishyaya and



Krimija Shiroroga (unilateral facial swelling, Headaches, Nasal congestion, Nasal discharge, Fever etc).<sup>[2]</sup>

Allopathic treatment requires high cost health approach and highly unaffordable for common and poor patients. Cost effective, potent and broad spectrum antifungal medicinal plants are describe in Ayurved Samhita. These Ayurvedic antifungal drugs can also use along with allopathic medicines to see the increased effectiveness of medicines in mucormycosis and to reduce complications which are produce after use of allopathic antifungal medicine.

## CONCLUSION

Some Ayurvedic plants having antifungal activity on mucormycosis. These medicinal plants having various chemical constituents which are useful in treating the fungal infection like mucormycosis.

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