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### Review Article

## Present Fungal Infection- And Prolific Drug Discovery Focused On Mucormycosis (Zygomycosis)

Dr. Mukesh H.Shukla

Ayushi Biotech, Gujarat, India.

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#### ABSTRACT

Since millennia, human beings are facing moderate to sever infections, either viral or bacterial. The present pandemic has now engulfed horrible structure and serious damages. The article predominantly focused on Mucormycosis (Zygomycosis) and its prolific drug through natural kingdom of plants and its active. In India there are more than 15000 cases and embarking faster. Patient with COVID19 history are more vulnerable and susceptible for Mucormycosis.

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**Corresponding Author:** *Dr. Mukesh H.Shukla, Ayushi Biotech, Gujarat, India.*

## INTRODUCTION

Viral and Fungal infections with present pandemic Mucormycosis and prolific drug discovery.

### Pathogenesis of mucormycosis:

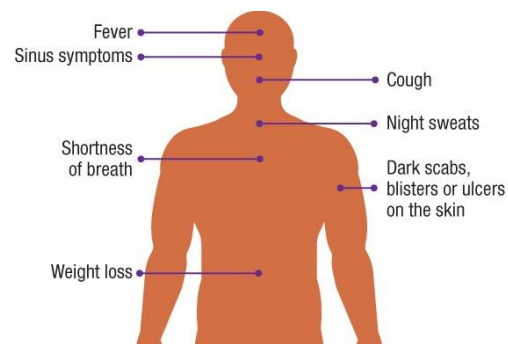
1. Mucormycosis is the general term that indicates any fungal infection caused by various genera of the class *Zygomycosis*.
2. Another term used in medical and lay publications that means the same is phycomycosis.
3. Mucormycosis (previously called Zygomycosis) is a serious but rare fungal infection caused by a group of molds called mucormycetes. These molds live throughout the environment. Mucormycosis mainly affects people who have health problems or take medicines that lower the body's ability to fight germs and sickness. It most commonly affects the sinuses or the lungs after inhaling fungal spores from the air. It can also occur on the skin after a cut, burn, or other type of skin injury.
4. Mild fungal skin diseases can look like a rash and are very common. Fungal diseases in the lungs are often similar to other illnesses such as bacterial or viral pneumonia. Some fungal diseases like fungal meningitis and bloodstream infections are less common than skin and lung infections but can be deadly.

Mucormycosis presents itself as either a respiratory or a skin infection. Signs of a related sinus or respiratory infection may include:, with a skin infection, Mucormycosis can develop within any part of your body. It may initially occur at the site of skin trauma, but it can quickly spread to another area. Be on the lookout for symptoms such as:

*Symptoms and signs first appear usually in the body area infected and may occur as follows:*

- Fever
- Headache,
- Reddish and swollen skin over nose and sinuses,

- Dark scabbing in the nose by eye(s),
- Visual problems,
- Eye swelling,
- Facial pain
- Coughing sometimes with bloody or dark fluid production,
- Shortness of breath,
- Diffuse abdominal pain,
- Bloody and sometimes dark vomits,
- Abdominal distension,
- Flank pain,
- An ulcer with a dark center and sharply defined edges, and
- Mental-status changes may occur



### People at Greatest Risk from Mold

People with asthma, allergies, or other breathing conditions may be more sensitive to mold.

People with immune suppression (such as people with HIV infection, cancer patients taking chemotherapy, and people who have received an organ transplant) are more susceptible to mold infections. People with weakened immune systems can develop invasive mold infections days to weeks after exposure to fungi that live in the environment. People with a weakened immune system, especially people receiving treatment for cancer, people who have had an organ or stem cell transplant, and people taking medicines that suppress the immune system, should avoid cleaning up mold. Children should not take part in disaster cleanup work.

### What are risk factors for Mucormycosis?

The following is a list of signs and symptoms (note that many authors prefer the term Mucormycosis instead of Zygomycosis since the majority of fungi when identified, are from the Mucoraceae family of fungi):

#### A. Rhinocerebral

**Mucormycosis: fever, headache**, reddish and swollen skin over nose and sinuses, dark scabbing in the nose by the eye(s), visual problems, eye(s) swelling, facial pain

#### B. Pulmonary (lung) C.

**Mucormycosis: fever, coughing** sometimes with bloody or dark fluid production, **shortness of breath**

**GI Mucormycosis: diffuse abdominal pain**, bloody and sometimes dark vomits, abdominal distension

**Renal Mucormycosis: fever, flank pain**

**Coetaneous Mucormycosis: initially**, reddish and swollen skin often adjacent to an area of skin trauma, that becomes an ulcer with a dark center and sharply defined edges

**Disseminated Mucormycosis: initially** may have any of the above symptoms; as the disease spreads to other organs, **headaches**, fever, and **mental status changes** occur

**Consequently, serious complications may occur, such as**

- Blindness,
- Meningitis,
- Brain abscesses,
- Osteomyelitis,
- Pulmonary hemorrhages,
- Gastrointestinal hemorrhages,

Caviar lesions in organs and eventually secondary bacterial infections, sepsis, and death. So far, the Black fungus has been reported among corona virus patients, but experts have warned that this fungal infection can happen to people without COVID-19 disease.

There are now more than 15000 cases in India and Gujarat is on top. There is major following

major medication provided in the conventional field besides other steroids and anti fungal medicines: Amphotericin B, Isavuconazole, Posaconazole.

It is noteworthy here that due to rampant use of steroids and antibiotics, the “Black Fungal” born. It is further expected by the huge community to have safe, effective and low cost medicines from the natural kingdom source. The rich experience and profound visionary signifies that “Ayurveda” may rescue the ailing humanity. At the same tenure it is more convincing to discover “Bioactive” safe and effective drug. The following natural drugs/its active compounds and the composition may be more prolific to safeguard the patient.

**The pathophysiology of novel drug discovery based on:**

*Mechanism of action:*

By inhibiting viral DNA polymerase; binding to specific cell-surface receptors and inhibiting viral penetration or uncoating; inhibiting viral protein synthesis; or blocking late stages of virus assembly\_HMPL-004 acts on multiple cellular targets in the inflammatory signal transduction pathways resulting in suppressed inflammation cytokine expression including TNF- $\alpha$ , IL-1 $\beta$  and IL-6. HMPL-004 was demonstrated to inhibit TNF- $\alpha$  and IL-1 $\beta$  production in cell-based assays. HMPL-004 is also able to inhibit NF-kB activation. NF-kB is a family of transcriptional factors that regulate a wide spectrum of genes critically involved in host defense and inflammation. The mechanism of action of HMPL-004 was further supported in laboratory IBD animal models. Treatment of IBD rats with HMPL-004 caused a significant drop in plasma cytokine concentrations, including TNF- $\alpha$  and IL-1 $\beta$ .

potent immunomodulatory agent in T cells, B cells, neutrophils, natural killer cells, dendritic cells, and macrophages In that regard, Peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) has been associated with anti-inflammatory effects. PPARs belong to the superfamily of nuclear receptors consisting of three genes that give rise to three different subtypes, PPAR- $\alpha$ , PPAR- $\delta$ , and PPAR- $\gamma$ .

Among them, PPAR- $\gamma$  is the most widely studied form.

#### Antiviral and Anti Bacterial Agents

Agents used in the prophylaxis or therapy of Bacterial and VIRUS DISEASES - Some of the ways they may act include preventing viral replication by inhibiting viral DNA polymerase; binding to specific cell-surface receptors and inhibiting viral penetration or uncoating; inhibiting viral protein synthesis; or blocking late stages of virus assembly

HMPL-004 acts on multiple cellular targets in the inflammatory signal transduction pathways resulting in suppressed inflammation cytokine expression including TNF- $\alpha$ , IL-1 $\beta$  and IL-6. HMPL-004 was demonstrated to inhibit TNF- $\alpha$  and IL-1 $\beta$  production in cell-based assays. HMPL-004 is also able to inhibit NF- $\kappa$ B activation. NF- $\kappa$ B is a family of transcriptional factors that regulate a wide spectrum of genes critically involved in host defense and inflammation. The mechanism of action of HMPL-004 was further supported in laboratory IBD animal models. Treatment of IBD rats with HMPL-004 caused a significant drop in plasma cytokine concentrations, including TNF- $\alpha$  and IL-1 $\beta$ .

#### Pharmacology

The pleiotropic effects of Curcuma longa against viruses arise from its ability to interact with various molecular targets, thereby triggering cellular signaling pathways such as apoptosis and inflammation.

Curcuma longa interacts directly with around 30 proteins, including DNA polymerase, thioredoxin reductase, focal adhesion kinase (FAK), protein kinase (PK), tubulin, and lipoxygenase (LOX). Moreover, Curcuma longa modulates intercellular signaling cascades which are essential for efficient virus replication such as attenuation of NF- $\kappa$ B and PI3K/Akt signaling. It also affects cellular post-transcriptional and post-translational modifications, thereby limiting the viral multiplication by interfering with crucial steps

in their replication cycle, including genome replication, and viral attachment

Mechanistically, Curcuma longa protects the lung by inhibiting inflammation and production of ROS through regulation of multiple signaling pathways engaging peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ). Curcuma longa has been shown to stimulate transcription of Nrf2 and thus enhance HO-1 expression *in vivo*, protecting alveoli from merging, inflating and enlarging, and decreasing inflammatory exudation of proteins to alveoli spaces after infection (Dai et al., 2018; Han et al., 2018).

It has been reported that Curcuma longa can inhibit pulmonary fibrosis. Thus, in paraquat-treated mice, collagen deposition in the lung causes diffused fibrosis, while treatment with Curcuma longa reduces collagen deposition and decelerates the development of pulmonary fibrosis (Chen et al., 2017). In the radiation-induced lung damage model, cytokine accumulation and collagen deposition occur in the interstitial space, concurrent with fibrosis of the lung tissue (Amini et al., 2018). However, *C.longa* reduces the expression of cytokines such as IL-4 and TGF- $\beta$ , inhibits the infiltration of macrophages and lymphocytes, and ameliorates fibrosis (Amini et al., 2018).

Cytokine storm syndrome triggered by viral infections is the culprit of death. It is exacerbated by unchecked regulation of the production of pro-inflammatory cytokines and ROS, leading to pneumonia, ALI, multiple organs failures, and eventually death. No effective therapy is available for the cytokine storm syndrome and associated lung and other organ failures. Curcuma longa is a natural plant extract with high safety and low toxicity such that people take it as a diet supplement, and growing evidence from preclinical studies demonstrates that it effectively inhibits viral infection, alleviates the severity of lung injury through offsetting the cytokine storm, inhibits subsequent fibrosis.

Piper nigrum:

Piper nigrum, a highly lipophilic alkaloid extracted from *Piper nigrum* significantly enhances the bioavailability of various nutrients through increased absorption.<sup>1</sup> P.nigrum does this by inhibiting enzymes that metabolize drugs and nutritional substances, stimulating amino acid transporters in the intestinal lining, inhibiting P-glycoprotein, and decreasing intestinal production of glucuronic acid.<sup>1</sup> Studies show increased absorption rates of 30%–60% for *cm* (from *cl*,<sup>2</sup> resveratrol,<sup>3</sup> CoQ10,<sup>4</sup>  $\beta$ -carotene,<sup>5</sup> and vitamin B6. In one study, the increased absorption of 2 g of *cm* with 20 mg of Piper nigrum was 2000%.<sup>2</sup> It is thought that Piper nigrum works by increasing blood flow to the gastrointestinal tract, thereby promoting active nutrient transport. The precise mechanism responsible for its absorption-enhancing activity is not fully understood. Piper nigrum passes through the intestinal barrier very quickly. It is theorized that it may function as an apolar molecule and form apolar complexes with nutrients and other compounds, thereby modulating membrane dynamics and thus helping to increase absorption across intestinal barriers.<sup>6</sup>

Glucuronyltransferase and hepatic arylhydrocarbon hydroxylase. It inhibits glucuronidation, a metabolic step by inhibiting the enzyme UDP-glucose dehydrogenase. It has also been proposed that Piper nigrum is a selective inhibitor of cytochrome P450 enzyme isoforms like CYP1A1, CYP1A2, CYP2C8, CYP2D6, and CYP3A4.

Thus Piper nigrum increases the bioavailability of parent aflatoxin B1 and produces chemoprotective effect against procarcinogens activated by CYP450B1

- Inhibit pulmonary cytochrome P450 activities
- Inhibit UDP-glucose dehydrogenase and UDP- glucuronyl transferase
- Shows antileishmanic activity
- Increases serum response of  $\beta$ -carotene

- Inhibit aflatoxins B1 (AFB<sub>1</sub>) biosynthesis
- Shows antimalarial activity
- Reduced the production of aflatoxins

Thermogenic action of piper nigrum *via* adrenal catecholamine secretion

- Inhibit monoamine oxidase
- Inhibit ascorbate-Fe<sup>++</sup>-induced lipid peroxidation
- Against oxidative stress induced carcinogenesis
- Modulated membrane dynamics and permeation characteristics
- Shows chemopreventive effect in carcinogenesis
- Inhibited mitochondrial oxidative phosphorylation
- Exerted protection against t-butyl hydroperoxide
- Protects cisplatin-induced apoptosis via heme oxygenase-1
- Potentiate hepatotoxicity of carbon tetrachloride in rats
- Inhibition /quenching of super oxides and hydroxyl radicals by piperine
- Reduces high fat diet induced oxidative stress
- Anti-metastatic activity of Piper nigrum on lung metastasis
- Inhibits platelet aggregation as a TXA<sub>2</sub>receptor antagonist
- Decreased mitochondrial lipid peroxidation
- Alleviates hypertension induced by NO synthase inhibition
- Reduced D-galactosamine induced hepatotoxicity
- Inhibited cholesteryl ester (CE) synthesis
- Enhances bioavailability of the tea polyphone
- Shows anti mutagenic activity
- Shows anti-thyroid activity
- Modulates hormonal and apo lipoprotein profiles

- Blood pressure lowering and effects of Piper nigrum
- Shows cytoprotective and immunomodulating properties
- Protects against neurodegeneration and cognitive impairment
- Inhibit mitochondrial dysfunction and cell death in PC<sub>12</sub> cells

#### Shows antibacterial and fungicidal activity

- Shows insecticidal activity
- Stimulates melanocyte replication *in vitro* and useful in treating the depigmenting Disease,
- vitiligo
- Shows antidiarrhoeal activity

*Nigella sativa* has been broadly studied in the last few decades and studies have reported that it possesses a number of medicinal properties and pharmacological actions. The seed of *Nigella sativa* (*N. sativa*) has been used in different civilization around the world for centuries to treat various animal and human ailments. Its main active constituent, thymoquinone, to be medicinally very effective against various illnesses including different chronic illness: neurological and mental illness, cardiovascular disorders, cancer, diabetes, inflammatory conditions, and infertility as well as various infectious diseases due to bacterial, fungal, parasitic, and viral infections-  
Antioxidant Antidiabetic Activity

#### Antihypertensive Activity

- Neuroprotective Effects
- Anti-Inflammatory and Analgesic Effects
- Antimicrobial Activity

#### Antifungal Activity:

*Nigella sativa* of different origins has been reported to possess moderate inhibitory action against pathogenic strains of yeasts, dermatophytes and nondermatophytic filamentous fungi along with aflatoxin-producing fungi. The *N. sativa* treatment targeted the cell wall, plasma membrane, and

membranous organelles, mainly in the nuclei and mitochondria as were evident in the morphology of these toxigenic fungi. Moreover, different extracts of black cumin and TQ exhibited powerful fungicidal activity against dermatophyte strains including *Trichophyton mentagrophytes* and *Microsporum gypseum* superior to fluconazole, but lesser than that of ketoconazole. Thymoquinone also arrested the growth of *Aspergillus niger* and *Fusarium solani* comparable to Amphotericin-B and was effective against *C. albicans*, *C. tropicalis*, and *C. krusei*. Similarly, as stated by Taha et al., the active constituent of black cumin such as TQ, thymohydroquinone, and thymol revealed potent antifungal effect against several clinically isolated fungal strains including dermatophytes, molds, and yeasts. As a potential candidate with multiple antimicrobial activities, *N. sativa* can also be explored as a natural preservative and food additive to protect foods from spoilage.

#### Antiparasitic Activity

- Anticancer Activity - Effects of *N. sativa* and thymoquinone against various types of cancer models and their effects on anticancer agents.
- Effects on Male Infertility - increasing spermatozoa counts, functionality, and sperm quality using antioxidants can improve fertility status.
- Evidence proves that some herbal medicines can reduce negative effects of oxidative stress by salvaging free radicals.
- Among the various traditional plants, *N. sativa* was found to exhibit remarkable antioxidant effect.

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