International Journal of Homoeopathic Sciences

E-ISSN: 2616-4493
P-ISSN: 2616-4485
www.homoeopathicjournal.com
IJHS 2022; 6(2): 27-32
Received: 07-10-2021
Accepted: 15-12-2021

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Usefulness of homoeopathic medicines in COVID associated mucormycosis: A scoping review

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DOI: https://doi.org/10.33545/26164485.2022.v6.i2a.534

Abstract
Rationale: The term mucormycosis (Black fungus) is the common name given to different diseases caused by fungi of the order mucorales. An unforeseen upsurge in Covid associated mucormycosis cases was seen during the second wave of Covid-19 in India in the months of April-June. An attempt has been made to systematically map the research done as well as to identify the existing gaps in knowledge regarding Mucormycosis in the field of homoeopathy through a scoping review.
Objective: To determine and synopsize the scientific evidence for the usefulness of homeopathic medicines in post covid-19 mucormycosis.
Methodology: A web-based literature search from medical databases (Pub Med, Science direct) and google search engine was carried out till December 2021.
Results: Total 5 literature review works could only be traced, discussing the role of homoeopathy in mucormycosis. The articles are review woks, containing literature information on homoeopathic approach in mucormycosis. Available grey literature is handful, aggregate 5 in number. No *in-vitro*, *in-vivo* or clinical study to analyze the antifungal effects of homoeopathic medicines on Rhizopus/mucor species was obtainable.
Conclusion: It is evident that the usefulness and effectiveness of homoeopathy in patients of mucormycosis has not been explored. This scoping review may form an excellent foundation to bring to the fore of the researchers in homoeopathy across the globe to study and understand the role that homeopathic medicines can play in the treatment of mucormycosis and likewise, other opportunistic fungal infections. Following these suggestions, research conducted may determine the importance and value of homeopathy in mucormycosis which may lead to probable scope for a systematic review.

Keywords: Homoeopathy, Covid associated mucormycosis, rhino-orbito cerebral mucormycosis, and black fungus

Introduction
The Covid -19 virus disease is extant among us. During the second wave of the pandemic, there was a sudden rise in cases of mucormycosis in India. Mucormycosis colloquially known as the deadly 'Black Fungus' is a common name given to different disease caused by the fungi of the order mucorales of the subphylum Mucoromycotina. Termed the name "mucormycosis" by the American pathologist R. D. Baker, it is a highly infectious, opportunistic fungal infection. The disease has an acute onset, rapid spread and produces serious angio-invasive involvement. It is a rarely occurring non-contagious disease having poor prognosis. These fungi moulds are ubiquitous, found in the soil, compost, decaying organic matter, air, etc. The infection is commonly seen in people having immune-compromised states. The high-risk patients include diabetics, patients with solid organ transplantation, having history of long-term corticosteroid use, neutropenia and iron overload. For people with weakened immune systems, mucormycetes spores cause an infection in the lungs or sinuses which spreads to other parts of the body [1, 2].
Paltauf coined the term 'Mycosis Mucorina' to a case of systemic infection with gastric and rhinocerebral involvement. The first evidence of phycomycotic infection in a diabetic patient was done by J. E. Gregory and colleagues in 1943 [3]. *Rhizopus oryzae* is the most common causative organism and is culpable for almost 70% of all cases of mucormycosis [4] followed by *Rhizopus microspores* and *Mucor circinelloides* [5, 6]. Depending upon the site and organ involved, mucormycosis can be classified into Rhino-orbito cerebral (ROCM), Pulmonary, Cutaneous, Gastro-intestinal and disseminated forms. The rhino-orbito cerebral form of the disease was the most common presentation in most of the reported patients, followed by pulmonary mucormycosis. The patients complain symptoms of eye/facial pain, numbness

followed by conjunctival suffusion and blurry vision, periorbital edema and proptosis. The etiology for the rising incidence of zygomycosis/ mucormycosis in patients recovering from coronavirus disease was mostly linked to the injudicious use of corticosteroids with hyperglycemia, poor maintenance of humidifiers during oxygen therapy due to the overburden of the disease in hospital set-ups in India. Mucormycosis is an uncommon but serious infection that complicates the course of moderate to severe cases of Covid-19 [2].

The primary route of infection is though air spore inhalation. These spores deposit in the paranasal sinuses and the lungs. Other less common routes include consumption of contaminated food, or invasion through abraded skin. The fungus can even be introduced through direct access, through contaminated tongue depressors and wooden applicators being used to mix drugs given to immunocompromised patients. After nasal inoculation, the fungus rapidly progresses to the neighboring tissues, including the orbit, and sometimes to the brain. Mononuclear and polymorphonuclear phagocytes are the main defense weapons to fight mucormycosis. They kill Mucorales by generation of oxidative metabolites and cationic peptides ie, defensins. Subsequently, the neutrophils inhibit proliferation of the fungal spores. In case of immunocompromised patients, these fungal spores bypass the oxidative metabolites and defensins and spread through the endothelial lining and disseminates into the body leading to extensive necrosis (Black eschar). Due to the use of corticosteroids and immunosuppressants these effects are greatly enhanced. Corticosteroids cause impairment in the neutrophil migration, ingestion, and phagolysosome fusion. In case of infection through the COVID-19 virus, a sequential increase in the serum ferritin levels occur, thereby increasing the intracellular iron (a favorable growth factor for mucor). In patients with systemic ketoacidosis there is a temporary halt of transferring to bind iron therefore the free iron levels increase in serum favoring the growth of the fungus [7-10]. Diagnosis is based on a detailed patient history, identification of characteristic symptoms and thorough clinical evaluation. The most enabling diagnosis is through CT and particularly MRI. Other diagnostic tools are fungal culture, histopathology, MALDI-TOF mass spectrometry, etc. [11] the general treatment approach in mucormycosis is surgical debridement with antifungal regime. Controlling underlying conditions such as hyperglycemia, diabetic ketoacidosis, and neutropenia is an important factor in treating the infection. Such an approach favors the prognosis of the disease.

Post covid-19 confection with mucormycosis can be prevented by taking suitable measures. The patients must not be housed in dusty areas and must wear a good mask and take proper precautions with maintaining a strict hand hygiene. There must be strict control of blood sugar. Judicious use of steroids with strict compliance to correct timing, correct dose, and duration by the treating physician. Strict vigilance over the use of only sterile/distilled water for humidifiers during oxygen therapy is recommended. All the hospital equipment's used for oxygenation such as nasal prongs, nasal cannula, masks for ventilation, etc. must be sterilized before each use and every day [12].

The incidence of covid associated mucormycosis cases reported in India till 7 June,2021 were 28200 with a contribution of approximately 70% cases globally [13]. Even prior to the coronavirus pandemic, mucormycosis was already far more prevalent in India than any other country. It is estimated to affect 14 per 100,000 people in India as compared to 0.06 per 100,000 in Australia [14]. Previous study reports from the hospitals all over the country have revealed presence of heavy mould spore counts in the hospital air. The chief reason is due to the hot, humid and tropical climate in India [2].

The rationale of the review was to systematically map the research done as well as to identify the existing gaps in knowledge regarding Mucormycosis in the field of homoeopathy. Based on which, following research questions were formulated:

1. What is known from homoeopathic literature about the treatment of mucormycosis?
2. Are there any published research work to establish the role of homoeopathic drugs in treatment of cases of mucormycosis?

The objective of the study was to identify and summarize the scientific evidence for the usefulness of homoeopathic medicine in post-Covid mucormycosis.

Materials and Methods

Scoping reviews are conducted to map existing literary work athwart a certain topic and to recognize the gaps and hereafter the research needs. They are used essentially in situations where little is known about a particular topic. Scoping reviews are supposed to be carried out systematically following an iterative approach and report the findings parochially to explore a topic. This scoping review was conducted following the PRISMA Extension for scoping review guidelines 2018. A web-based literature search from medical databases (Pub Med, Science direct) and google search engine was carried out till December 2021. (Figure 1)

The inclusion and exclusion criteria were

Inclusion criteria

1. Records where details of role of homoeopathic medicines in mucormycosis were given
2. Records with full text available were included.
3. Records published in English language were included.

Exclusion criteria

1. Records where details on homoeopathy or homoeopathic medicines were not available were excluded.

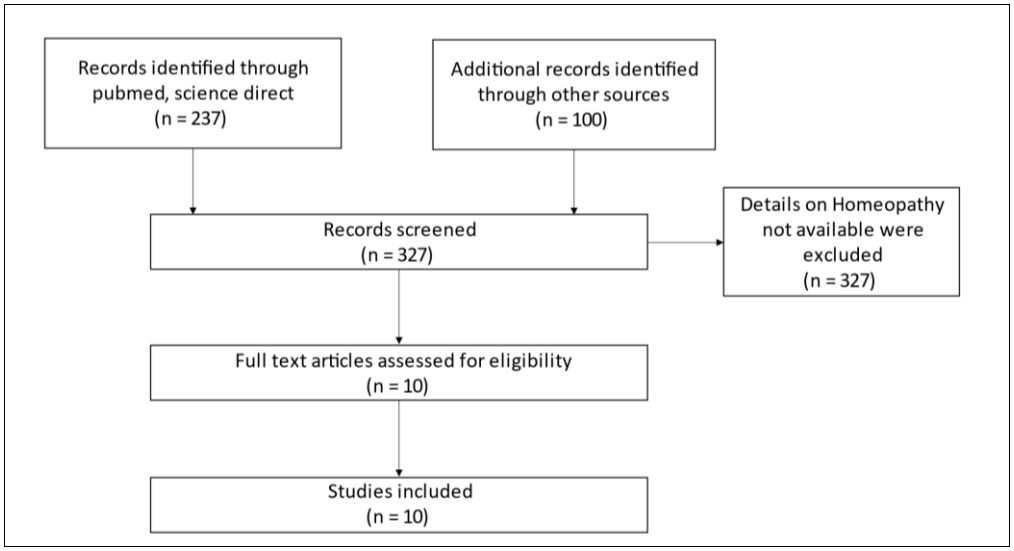

Fig 1: PRISMA Flowchart

Result

Total 5 literature review works could only be traced, discussing the role of homoeopathy in mucormycosis (Table 1). Available grey literature is handful, aggregate 5 in umber. (Table 2). No *in-vitro*, *in-vivo* or clinical study to analyze the antifungal effects of homoeopathic medicines on rhizopus/mucor species was obtainable.

Table 1: List of peer articles retrieved through web search

Author	Year	Journal	Aim	Method
Javed D, Dixit AK, Vats H *et al.* [15]	2021	International Journal of Health Sciences and Research	To investigate the role of Ayurveda and Homoeopathy in the treatment of mucormycosis	Narrative review
S.R. Sharma, Bindu Sharma [16]	2021	Homoeopathic Links	N/A	Editorial
Singh M. [17]	2021	International Journal of Science & Research	To study Mucormycosis and its homeopathic approach	Literature review
Gond BP. [18]	2021	International Journal of Homoeopathic Sciences	To get an overview of etiopathogenesis of Mucormycosis and its homoeopathic approach	Literature review
DwivediAK. [19]	2021	International Journal of Scientific Review	How homoeopathic medicines can help treat /cure Black fungus/ Mucormycosis in patients under Allopathic treatment	Literature review

Table 2: List of Grey literature available

Organisation	Author	Publication	Date	Notes
Ministry of AYUSH, GOI [20]	Not applicable	Information for Homoeopathy Practitioners for Symptomatic Management of Suspected and Diagnosed cases of Mucormycosis	May 21, 2021	Includes general guidelines for Homoeopathic doctors to provide symptomatic management in cases of Mucormycosis
Dr Willmar Schwabe [21]	Dr. Aditi Sharma	White versus Black Fungus: Is white Fungus more dangerous than Black Fungus	July 14,2021	Provides information on both white fungus and black fungus, gives a comparison between the two fungus groups with indications of homoeopathic medicines
Homeocare4u [22]	Dr. Vishnu Singh	Top 5 homoeopathic remedies for Black Fungus or Mucormycosis	Not mentioned	Give a list of homoeopathic medicines for mucormycosis based on the general symptoms
Homoeopathic Dr Makkar Family Clinic [23]	Dr. G. S. Makkar Sukhmani	Mucormycosis Black Fungus Zygomycosis Homoeopathic treatment	Not mentioned	Mentions a detailed description of mucormycosis including the pathogenesis and symptomatology. Also details the group of homoeopathic medicines suitable in such infections
Souls [24]	Dr. Divya Mishra	Mucormycosis management with a Homoeopathic approach	June 8,2021	Provides a brief history, current scenario and types of mucormycosis with a list of homoeopathic medicines in mucormycosis

The common medicines reviewed for their utility in mucormycosis, as per the literature retrieved from the peer review studies have been enlisted (Table 3).

Table 3: Common group of medicines reviewed under the peer review articles

Acidum floricum	Kali iodatum
Acidum nitricum	*Merc iod flavum*
Acidum benzoicum	*Merc iod rubrum*
Arsenic album	*Merc solubilis*
Aurum metallicum	*Phosphorus*
Carbo animalis	*Secale cornutum*
Cinnabaris	*Sulphur iodatum*
Condurango	*Thuja occidentalis*
Hippozaeninum	*Tuberculinum*
Kali bichromicum	

Discussion

It was evident from the results of the review, that the role of homoeopathic medicines in mucormycosis is unfathomed. The review could not trace any clinical studies (RCTs, case series/case reports) and observational studies. The articles accessible were solely review of the mucormycosis basic pathophysiology and approach of homoeopathy in treating the disease. Indications of homoeopathic medicines from textbooks have been illustrated in the reviews based on symptom similarity. Hypothetically, to conduct studies on patients suffering from mucormycosis are certainly difficult owing to the rapid and fulminating growth of the fungus and availability of isolated infections. This is the probable reason for the scarcity of evidence on effectiveness of homoeopathic medicines in cases of mucormycosis clinically. However, the *in-vitro* effects have also not been observed.

Till date, the extent of available research studies with homoeopathic medicines in case of fungal infections is limited to the effects of inhibiting fungal growth, *in-vitro*. Few clinical trials establishing the role of homoeopathic medicines on the common dermatophytes and candida infections have been done. As perceptible from past works, homoeopathic medicines possess antifungal properties. *Sharma B.* in 2019, conducted an *in-vitro* study on Candida albicans to study the effects of homoeopathic mother tinctures of *Syzygium jambolanum, Ficus religiosa, Ocimum sanctum and Allium cepa*. Conventional drug Ketoconazole (10 µg/ml) was used as control. The fungal sample were taken from 60 patients suffering from Candida infection. The fungal culture was procured as lyophilised freeze-dried culture strain and was used to evaluate the antifungal activity using the agar disc diffusion method. The study concluded the antifungal properties of these drugs by measuring the zone of inhibition. The homoeopathic mother tincture *S. Jambolanum* had maximum zone of inhibition, even more than Ketoconazole [25].

Shinde CH, Anand PK, Kunchiraman BN et al, 2018 tested the *in-vitro* effects on *C.albicans* through anti-candida assay using agar-diffusion method, minimum inhibitory concentration values and germ tube inhibition method. The homoeopathic medicines *Azadirachta indica, Cinchona officinalis, Zincum metallicum, Iodium, Selenium, Sulphur, Acidum Benzoicum, Phosphorus, Acidum Sulphuricum* and *Zingiber officinale* were tested in 6C, 12C, 30 C, 200 C, 1M potencies for their effects. [26] Similar previous studies by different researchers to analyze the *in-vitro* effects of homoeopathic medicines in various potencies have concluded results favoring the use of homoeopathic medicines on *Candida albicans*. The drugs that have been worked on are *Sulphur, Holarrhena antidysenterica, Eucalyptus globulus, Apis mellifica, Kali iodatum, Mezereum, Petroleum, Tellurium, Sulphur iodatum, Graphites, Sepia, Silicea* and *Thuja occidentalis* [27-29].

In another study on the commonly occurring *Aspergillus niger*, homoeopathic medicines *Allium cepa, Allium sativum, Caesalpinia bonducella, Calotropis gigantean, Cassia angustifolia, Eucalyptus globulus, Ficus religiosa,* Holarrhena antidysenterica, *Kalmia latifolia, Ocimum sanctum, Ruta graveolens, Syzygium* jambolanum, Thuja *occidentalis, Terminalia chebula,* and Zingier *officinalis* have been investigated for their antifungal properties [30]. Few more such studies on other fungus have been carried out showing effective results with homoeopathic drugs in *in-vitro* models. A similar approach may be beneficial in elucidating the utility of homoeopathic medicines in *Rhizopus* and other mucormycosis causing fungal species as well.

Conclusion

Homoeopathy is a well-established form of alternative therapy globally. Homoeopathic Materia medica is enriched with medicines that help to cure any disease occurring in nature. Being a rarely occurring infection, much evidence on the role of homoeopathy in mucormycosis has not been yet established. As fungal infections are so common in India due to hot and humid climate, more work in homeopathy will certainly open doors to some unexplored arenas. Mucormycosis, being a rapidly progressing disease and having high incidence in India, the study of homoeopathic drug action on mucormycosis will be advantageous both for the patients and the system of medicine. In such a global crisis where, every individual is affected in some way, use of natural healing art of homoeopathy can help rejuvenate naturally.

Conflict of interest: The author declares no conflict of interest.

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