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Effect of Ayurvedic Intervention as an adjunct therapy in Post COVID-19 Mucormycosis (PCM): A non-randomized parallel group study

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PII: S0975-9476(22)00131-0

DOI: https://doi.org/10.1016/j.jaim.2022.100672

Reference: JAIM 100672

To appear in: *Journal of Ayurveda and Integrative Medicine*

Received Date: 3 November 2021

Revised Date: 25 April 2022

Accepted Date: 19 October 2022

Please cite this article as: Madikonda Pk, Perugu SB, C H R, Effect of Ayurvedic Intervention as an adjunct therapy in Post COVID-19 Mucormycosis (PCM): A non-randomized parallel group study, *Journal of Ayurveda and Integrative Medicine*, https://doi.org/10.1016/j.jaim.2022.100672.

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Running title: *Adjunct therapy Ayurvedic therapy for PCM*

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Permissions:

2. **Ministry of Health & Family welfare, Government of Telangana(Memo 4609/E/2021)**
3. IEC- DRBRKRGAC/2021

Author role declaration

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Concepts	√	√	√
Design	√	√	√
Definition of intellectual content	√	√	√
Literature search	√		√
Clinical studies	√	√	√
Experimental studies	√	√	√
Data acquisition	√		√
Data analysis	√	√	√
Statistical analysis	√	√	√

Manuscript preparation	√	√	√
Manuscript editing	√	√	√
Manuscript review		√	√

Conflicting Interest (If present, give more details): Nil

Acknowledgement: We are highly indebted to the support we received from Commissioner Department of AYUSH, Dr. Alagu Varsini IAS for the initiation and monitoring at every step of study. We also acknowledge the support of Dr.T.Shankar, Superintendent Government ENT Hospital Koti, Hyderabad, Dr.Manish Gupta, Associate Professor, ENT hospital, Hyderabad for providing facilities to work at Government ENT hospital, Hyderabad for conducting of the study. We thank Dr. V. Balakrishna, Drug inspector, Dept of Ayush, Telangana, Dr. Saketh ram, Research officer, NIIMH-CCRAS, Hyderabad. We convey our thanks to Dr. Ak. Sailaja. Head Dept of Pharmaceutics, RBVRR, women's college of pharmacy, Hyderabad for conduction of lab analysis of antifungal properties of Ayurveda intervention drugs. The contribution of following PG scholars Department of Shalakya, BRKR Government Ayurvedic college, Hyderabad Dr. Paidipala Girija Shree, Dr.Mangilipally Divya, Dr.A. Mallikarjun, Dr. Nalini Yadav, Dr. Punnam ramya kumari is worth mentioning as they worked in the wards maintaining case records and follow-up studies of patients. Internees Dr Akshay Tandley, Dr.P. Mounika priyadarshini Dr.D.Anagha , Dr Hima vani ,Dr Himanshi Choudhary, Dr.P Pravalika yadhav and Dr Varthya mohan naik extended support in data collection.

Financial support and sponsorship: Entire financial support for the project has been extended by Department of AYUSH, Telangana. [Grant number: Letter no 446/C/2021]

Effect of Ayurvedic Intervention as an adjunct therapy in post COVID-19 Mucormycosis (PCM): A non-randomized parallel group study.

Abstract

Background: The Ayurveda therapy is often used as an adjunct to conventional allopathic treatments for management of chronic disorders including life threatening infections such as post COVID-19 Mucormycosis (PCM).

Aims/ Objectives: The aim of the current study is to evaluate the role of adjunct Ayurveda therapy (AAT+CAT) over conventional Allopathic therapy (CAT) in the prevention of progression of oral/ orbital / neural extension of PCM.

Material and methods: A non-randomised parallel group interventional study was on a sample of 92 cases of PCM, sorted into two groups i.e. group A (n=46; AAT+CAT) and group B (n=46; CAT/controls). The group A received AAT (lab-tested standardised regimen) while simultaneously receiving conventional antifungal measures (or CAT). The outcomes assessed were clinical symptomatic grading score, Nasal endoscopic examination for patency of sinuses, Progression or extension of disease from sinuses to maxilla, orbit and brain, need of additional surgical interventions and antifungal medication after study period, adverse drug reactions and mortality.

Results: The group A (AAT+CAT)) had shown extension free PCM in 86.96 % (n=40) as opposed to 41.3% (n=19) in group B (CAT), No surgical interventions were needed in 89.13 %(n=41) in group A vs. 60.87% (n=28) in group B. Around 69.5% (n=32) in group A vs. 4.37% (n=2) in group B did not need antifungal medication. The safety of both arms of the therapy has been determined by liver function and renal profile which are with in normal range in both groups.

Conclusion: Adjunct Ayurveda therapy (given along with routine medical therapy) for PCM showed a better cure and reduced disease progression after a trial period of 45 days and in the extended observational period of three months. AAT+CAT regimen is not only therapeutically effective, but also safe and economical option to consider for PCM.

Keywords: Ayurveda, COVID-19, Mucormycosis, Complementary Medicine, Medicine, Alternative, AAT (Adjunct Ayurveda Therapy), CAT (Conventional Allopathy therapy)

Introduction

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and is the reason for the on-going pandemic. Since its detection, in December 2019 in China, an adherence to one a standard pathophysiology, management, or occurring complications were noted. [1] The Post COVID-19 Mucormycosis (PCM) or 'black fungus' (local term), is an infection that causes necrosis in the head and neck regions (affecting the nose, paranasal sinuses, eyes, facial bones, and the brain). [2] The PCM is associated with a high morbidity and mortality accountable to delayed diagnosis and rapid progression. The Indian Health Ministry has advised all states to declare mucormycosis an epidemic. Patients with uncontrolled diabetes, a dysfunctional immune system due to Covid infection and injudicious use of corticosteroids could be largely responsible for this ailment. The central/ state government authorities tried to cope up with this rapidly progressive ailment with a conventional approach of providing possible antifungal measures following initial surgical debridement.[1-3]

The Ministry of Health & Family Welfare of Telangana State in an unprecedented move officially permitted adjunct Ayurveda intervention with conventional Allopathic antifungal management for Mucormycosis at two major allopathy hospitals of Hyderabad with effect from

26/5/2021.[4] In this regard, more than 130 patients of PCM have been provided adjunct Ayurveda intervention at Government ENT hospital, Hyderabad, TS, India.[4] According to the statement issued by Union Health ministry of India on 22nd June, 2021, a total number of 45, 374 cases of Mucor mycosis were reported in the country and out of which 4332 deaths have occurred due to the ailment. The reported Mortality rate is around 9.6%, unlike the previously observed mortality associated with non COVID-19 related mucormycosis which was around 50 to 80%. As per the data available on 21st July 2021, Telangana reported 2538 cases of PCM with a lesser mortality rate than expected as compared to the other states, owing to prompt actions by the government of Telangana to provide adjunct therapy with Ayurveda for Mucormycosis.[6]

Though rate of death is lesser than the anticipated figures, PCM still remains to be a huge cause of concern, due to its rapidly progressive nature and its extension to orbits causing permeant vision impairment enforcing an inevitable enucleation in some of the patients. The identification (of diabetes / steroid supressed cases)/ risk factors etc) and early addressing is needed for dealing with PCM. [7] The role of Ayurveda in providing a treatment plan for COVID-19 is well documented in literature. [8] The role Ayurveda for the management of PCM is extensively discussed in reviews. [9,10] A case report highlighted that nasal spray irrigation employed in Ayurvedic practice, aided in prevention of rhino-orbital PCM progression.[11] However, the utility of Ayurveda based adjunct therapies for PCM, explored in a clinical study are sparse in literature and are need to be reported.

Aim:

The aim of the current study is to evaluate the role of adjunct Ayurveda therapy (AAT) given with conventional Allopathic therapy (CAT) over CAT alone in the prevention of progression and oral/ orbital / neural extension of PCM.

Objectives:

To compare namely the *nasal crusts and synechiae, clinical symptoms /grading,* need /stoppage of Antifungal medicine, disease progression, additional surgical requirements, Mortality and Adverse effects, and bio-chemical parameters between groups that received adjunct Ayurveda therapy (AAT) with conventional Allopathic therapy (CAT) over CAT alone in post COVID-19 mucormycosis (PCM) cases.

Methodology:

Study settings:

A non-randomised parallel group interventional study (Quasi-Experimental Design) was conducted at Dr. BRKR Government Ayurvedic College, Hyderabad with collaboration of Government ENT Hospital, Hyderabad from of 26th May 2021 to 26th July 2021. The study was conducted on on a sample of 92 patients with Post COVID-19 mucormycosis (PCM).

Sample size and sampling:

A sample 92 was obtained by non-probability sampling (conventional method) and sorted into two groups i.e. group A (n=46; AAT +CAT was given) and group B (n=46; CAT was given/ taken as controls). The participants in group A received AAT (lab-tested standardised regimen) while simultaneously receiving conventional antifungal measures (or CAT). The sampling technique used was consecutive systematic sampling (every first case that fits the set criteria was considered to be sorted into group A and the next into group B, until the sample size was reached). The treatments were not blinded i.e. those who consented for ATT were only taken for group A, followed by equal sampling in group B (CAT/ controls). Thus, non-randomised

nature of design is explained. Random allocation to ATT+CAT or CAT groups was not considered, owing to patient consent and concerns over novel treatments during pandemic.

The study was approved by Institutional Ethical Committee, of Dr BRKR Government Ayurvedic College, Hyderabad. (Reference no: IEC/DRBRKARGAC 2020-21; dated 24/05/2021). A written informed consent was obtained in English and local langue (Telugu) for all the participants before commencing of the study.

Study criteria:

The patients between age group 18 years to 70 years of either gender, who diagnosed PCM, with a willingness to participate in the study (by providing a duly signed consent form), those who have been taking Conventional allopathy treatment (with Amphotericin B for three days following FESS (functional endoscopic sinus surgery) for Mucormycosis as per the protocol of Government ENT Hospital, patients who are willing to use Ayurveda medicine at least for thirty days, patients with mild to moderate Mucormycosis with Nasal, oral involvement clinically with or without orbital involvement were included in the study.

The cases of Mucormycosis presenting with complications such as stroke and seizures, known cases of PCM with CNS involvement or Pulmonary Mucormycosis, the participants who failed to use AAT continuously for thirty days and those unwilling and uncooperative for study were excluded.

Patients and groups

In the group A in which AAT+CAT was given, 46 patients could complete study period of 45 days duration and were observed for a total period of three months. Similar number of patients (n=46) were included in group B (controls/ CAT was provided). There were 26 dropouts from the group A. All of them dropped from the study within two to five days of starting the

intervention. The reason for drop out is largely due to the apprehension regarding the use of both Ayurveda and allopathy at the same time. Though 62 patients were recruited under control group, 16 patients were excluded as their initial MRI findings are suggestive of CNS spread at the time of registration. All the registered patients underwent a mandatory FESS (functional endoscopic surgery) with a three day intervention with Amphotericin B. All the patients there after were kept on Posaconazole in a dose of 300mg per day.

Need of the control group: Conventional allopathy intervention is an established therapy for Mucormycosis. Therefore the efficacy & advantage of Adjunct Ayurveda intervention will be known only when it is compared with the same given in control group.

Interventions

All the participants that fit the criteria of the study and diagnosed with PCM underwent initial FESS (functional endoscopic sinus surgery) and mandatory administration of Amphotericin B for three days. The following outcomes were measured ain both groups. Specifically, the group A participants received FESS +Amphotericin B for three days, Posaconazole for at least two weeks along with AAT. The group B (controls) received only CAT after common routine (FESS +Amphotericin B for three days + Posaconazole as per the advice of ENT doctors). The AAT used for the group A subjects is summarised in Table 1. The antifungal efficacy of the Ayurveda medicines used was pre-tested in laboratory settings.

Table No 1 – Adjunct Ayurveda Intervention used in the present study

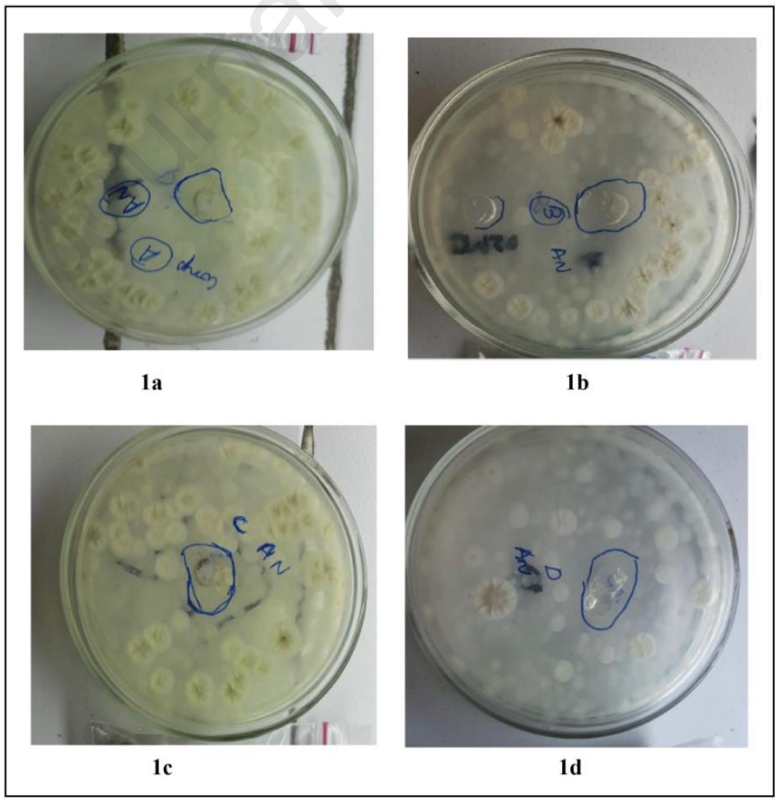
	Principle /rationale behind Ayurvedic intervention medicine	**Name of the compound Ayurveda medicine***	**Dosage**

1	Effective against fungal ailments	1. Gandhaka rasayana (3,4) 2. Kaisora guggulu(5-10)	500 mg tab thrice a day after food 500mg tab thrice a day after food
2	Aiding in Symptomatic improvement, Anti inflammatory	3. Dasamula katutrayadi kashayam 4. Vyoshadi vati	One gram tablet once a day 500 mg 2 tab twice day-chewable
3	Immune promotive Anti hyperglycemic	5. Vasanta kusumakar ras 6. Nishamalki	One tab once a day 500 mg 2 tab twice a day
4	Drugs which improve local hygiene (Topical use)	1. Surasadi gana taila nasya (11, 12) 2. Triphala, Daru haridra Kashaya for gargling (Kavala) 3. Fumigation of sinuses with herbal Sticks made of Trifala & daruharidra (Dhuma Nasya) (13-14)	2 drops in each nostril for local application once a day morning 50 gm of the powder to be boiled in a 400ml of water and reduced to 100 ml. for gargling in mouth with closed lips for 10 min/ twice a day (Kavala) Fumes from the herbal sticks made of Trifala & Daruharidra powders (Berberis Aristata)

**as Vata-kapha symptoms were more, Ushnodaka was advised as Anupana.*

Analysis of antifungal activity of the Ayurveda Intervention drugs: The anti-fungal activity of Kaisora guggulu, Gandhaka rasayanam, Dashamula Katutrayadi kashayam, Trifala and Daruharidra powder was tested against *Aspergillus niger*, *Candida albicans* and *Rhizopus*

oryzae. Anti-fungal activity studies were performed at Laboratory College of pharmacy, Barkatpura, Hyderabad. The method employed was Agar well diffusion method. Clotrimoxazole solution was taken as standard. From the results it was observed that Kaisora guggulu was exhibiting antifungal activity against *Aspergillus niger* with a zone of inhibition of 8 mm. Gandhaka rasayanam was exhibiting antifungal activity against *Aspergillus niger* with a zone of inhibition of 14 mm. Dashamula Katutrayadi kashayam was exhibiting antifungal activity against *Aspergillus niger* with a zone of inhibition of 13 mm. Trifala and Daruharidra powder was exhibiting antifungal activity against *Aspergillus niger* with a zone of inhibition of 16 mm. Whereas the standard Clotrimoxazole solution was exhibiting 18mm. Dashamula Katutrayadi kashayam was also exhibiting anti-fungal activity against Candida albicans with a zone of inhibition of 10 mm. Whereas the standard was showing 25 mm. (See figure 1a-d)



1a 1b

1c 1d

Figure 1- Laboratory analysis (antifungal activity) of Ayurveda intervention against *Aspergillus nigger*: 1a, 1b: Kaosora gugullu and Gandhaka rasayana- Zone of inhibition (ZOE) *at 8mm and 14mm respectively; 1c,1d: Dasamula katutrayadikasayam and Daruharidra churna- ZOE at 13mm and 16mm*

The above report showed that Kaisora guggulu, Gandhaka rasayanam, Dashamula Katutrayadi kashayam, Trifala and Daruharidra powder were exhibiting good anti-fungal activity against *Aspergillus niger*. Dashamula Katutrayadi kashayam was also effective against Candida albicans. Surasadi taila couldn't exert antifungal activity in laboratory probably due to its lesser solubility in the medium.

Outcomes assessed:

1. ***Examination for nasal crusts and synechiae:*** Following the FESS, all were examined for presence of nasal crusts and synechiae at every fortnight. The observations and findings made by ENT doctors were documented in their case records. Patency of all sinuses and absence of nasal crust is an important indication for disease clearance from the channels of nose, which was found to be in accordance to the clinical observations and symptomatology improvement. However in some cases Synechiae, of the Sino nasal cavity may occur following Endoscopic nasal surgery(ENS) also referred as DNE (Diagnostic nasal endoscopy).

2. ***Clinical symptoms and grading:*** This was done based on MRI and clinical grading systems to compare the scores before and after interventions. MRI of sinuses and brain is an important guideline to establish extent of disease progression and remission. All the registered patients were graded based on their presenting clinical symptoms and MRI and clinical symptoms for intergroup assessments. See Table 2 for MRI based grading

Table 2: Magnetic resonance imaging (MRI) based grading (*as per grading Government ENT hospital, Hyderabad)*

S.no	Site of spread	Grading
1	MRI of evidence of only Sino-nasal disease	Grade 1
2	MRI suggestive of Sino-nasal-maxillary disease	Grade 2
3	MRI suggestive of disease limited to rhino-orbital involvement	Grade 3
4	MRI suggestive of rhino-orbital-cerebral disease	Grade 4

3. **Use /Stoppage of Antifungal medicine**: In both groups, patients were enquired for their continuity or stoppage of antifungal medication. Those with both clinical improvement and patent sinuses are advised to stop antifungal oral medicine Posaconazole. But repeated hospital admissions and requirement of additional surgical interventions such as maxillectomy and orbital exenteration necessitates the need of using Liposomal Amphotericin B and/or Posaconazole for an extended period, which in a way adds to the financial burden both to patient and on health care system.

4. **Disease progression**: To be able to prevent progression of disease has been one of the primary objectives of Adjunct Ayurveda therapy intervention. This has been assessed on the basis of disease progression/ extension from sino nasal to oral cavity, orbits and CNS. Post therapy MRI has been carried out in some of the patients also revealed post therapy disease status and its extension.

5. **Additional Surgical requirement**: Those who either doesn't respond to therapy the disease may spread to oral cavity or orbit enforcing either maxillectomy or enucleation depending on the severity. Lesser the need of any further surgical needs during and after the study period, the greater the efficacy of intervention.

6. **Mortality & Adverse effects**: Though Mortality has been also taken as one of the

parameter, as discussed earlier, reported rate of death in PCM has been observed to be less than non COVID related mucormycosis. All the patients also have been enquired for any drug intolerance & adverse drug reaction in both groups.

7. **Bio-chemical parameters:** To witness any deleterious effects on liver, kidney, and bone marrow, by conducting and comparing before and after biochemical parameters such as serum creatinine, blood urea, Liver function tests.

Trail monitoring

The study was monitored by principal investigator (PI) who had actively communicated with a site staff (Research assistant, at ENT hospital who collected data). The Research assistant was reviewed by PI weekly for the procedures and records. The verification of the accuracy of data collected was ensured by co-investigator (A professor in Ayurveda). The results data reporting, drafting and review of work was done by a guarantor (A Senior professor in Ayurveda).

Observations:

Ninety two patients of PCM had a mean age of 46.3 ±10.2 years. Eighty one patients (88%) were aged between 31-60 years. Most patients were male (n = 74) and the major co-morbidity has been diabetes mellitus in 83 patients (90%). Thirty six patients (39%) were newly diagnosed as diabetic during COVID attack. A total of 59 patients (64.1%) received steroid therapy and 33 patients (35.8%) didn't have any history of steroid use during COVID attack. Oxygen support was extended in 42 patients (45.6%) and 50 patients reported that they did not use oxygen during covid period (54.3%), however none of the patients required ventilator support. The interval between COVID-19 recovery and, hospitalisation for Mucormycosis was between 11-25 days in 54.6% patients.

As per the initial MRI Screening 58.7% had Sino nasal mucormycosis at the time of admission, followed by 31.5% with rhino orbital involvement. Nineteen patients have initial clinical symptoms related to

Sino nasal mucormycosis: grade 1-(20.65%), and a maximum of 48.91% of patients have symptoms related to rhino maxillary (grade 2), while 28 patients have presented with symptoms related to rhino orbital involvement : grade 3 (30.4%). Even though majority of patients have evidence of Sino-nasal mucor mycosis as per their MRI findings, most of patients presented with clinical symptoms related to both nose and oral cavity. The initial mean of disease severity index, which has been ascertained, based on MRI of PNS/ Brain and Clinical grading is same in both groups indicating matching of case vs control. Over all 36 patients presented with pan sinusitis (40.44%). which was followed by and Maxillary & Ethmoidal sinus involvement.

Results:

(i) ***Examination for nasal crusts and synechiae:*** Attempt has been made to document the findings for presence of nasal crust, synechiae or patent sinuses, through periodical DNE. 71.4% (n=33) of group A (AAT+CAT) subjects who recovered from clinical symptoms presented with patency of sinuses without any trace of crust or synechiae. This was only 6.5% (n=3) in control group. The DNE examination was deemed as 'not clear' in 28.26 % (n=13) and 82.6% (n=38) in group A and B respectively. In 5 patients in group B, the details of DNE were not available as they have not turned up for their final follow up. The clinical symptoms of patients with patent sinuses are very less compared to those with presence of crust and synechia. Therefore the Endoscopic nasal evaluation could be taken as one of the standard parameter for clearance of Mucor mycosis. Figure 2 shows outcomes of a clinical case treated with AAT+CAT.

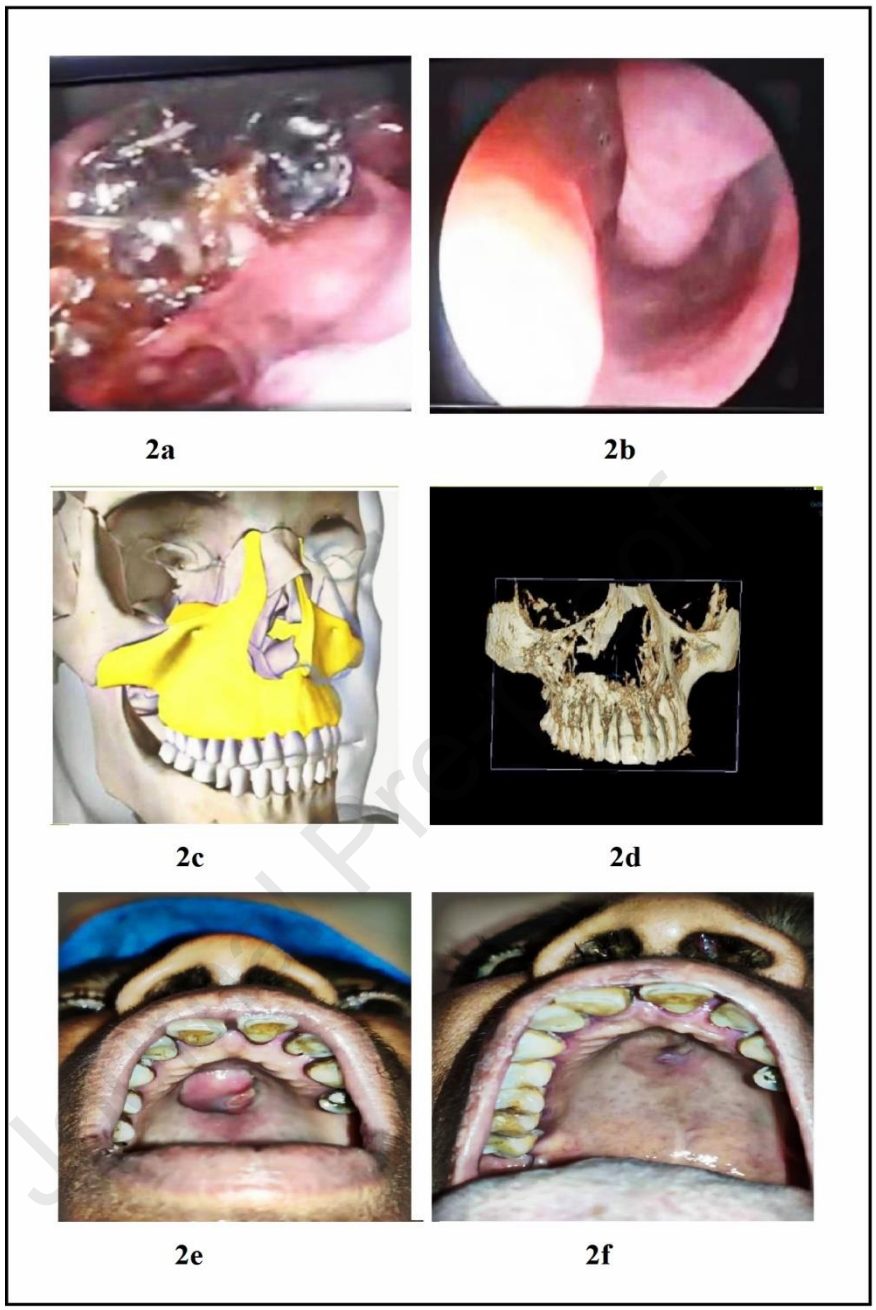


Figure 2- The observations of a clinical case in (ATT): ***2a: pre-treatment DNS (showing crusts; 2b:post-treatment DNS (patent sinus); 2c: - showing normal maxillary bone ; 2d: radiographic appearance of effected bone after PCM in Control group (CAT); 2e: pre-treatment PCM case with palatal ulceration; 2f: post-treatment PCM case with resolution of ulceration after Ayurveda adjunct therapy.***

(ii) Clinical symptoms and grading: Post therapy MRI of PNS/Brain has been performed in 15 patients with persistent symptoms. Post therapy MRI showed CNS extension in 19.7% (n=9) in control or group B as compared to only in 6.6% (n=9)

in Adjunct therapy or group A. Clinically 43% (n=20) and 13% (n=6) showed good and excellent outcomes in group A as opposed to 19.6% (n=9) and 2.2% (n=1) in group B (controls) See table 3.

Table 3: Comparison of improvement in clinical grading after therapy between groups

Clinical Grading Result	Group B (CAT)		Group A (AAT+CAT)	
	No.	%	No.	%
Very Progressive	4	8.7	0	0
Progressive	5	10.9	0	0
Stable	21	45.7	10	21.7
Good	6	13	10	21.7
Very Good	9	19.6	20	43.5
Excellent	1	2.2	6	13
Total	**46**	**100**	**46**	**100**

(iii) **Use /Stoppage of Antifungal medicine**: Around 69.5% (n=32) in AAT+CAT group vs. 4.37% (n=2) in control group did not need antifungal medication. Around 30.43% (n=14) in group A (AAT+CAT group) and 95.6% (n=44) in group B (CAT) were still using antifungal medications.

(iv) **Disease progression**: Disease progression has been measured in terms of oral extension of the disease from nasal sinuses to oral cavity, eye and brain. In the group A (AAT+CAT) only 10.8%(n=5) underwent partial maxillectomy and the MRI of one patient revealed CNS extension. In group B (control/ CAT) over all 58.6%(n=27) suffered with some or the other form of disease extension and 9 were found to have CNS extensions. Around 30.4%(n=14) from control group underwent

maxillectomy compared opposed to 10.8%(n-5) in adjuvant group. In Four patients of the control group the disease invaded orbits enforcing enucleation. While none from the adjunct therapy group have any form of intra orbital extension. Overall, the group A (ATT+CAT) had shown extension free PCM in 86.96 % (n=40) as opposed to 41.3% (n=19) in group B (CAT). No surgical interventions were needed in 89.13 %(n=41) in group A vs. 60.87% (n=28) in group B. See Table 4 and Figure 3,4

Table 4: Comparison of the disease progression in both groups

Sl. No	Affected Part/ Region	Group A (AAT+CAT)		Group B (CAT)	
		n	%	n	%
1	Maxilla/ oral cavity Extension	5	10.87	14	30.43
2	Intra-orbital Extension	0	0	4	8.7
3	Intra-cranial Extension	1	2.17	9	19.57
4	No Extensions	40	86.96	19	41.3
Total		**46**	**100**	**46**	**100**

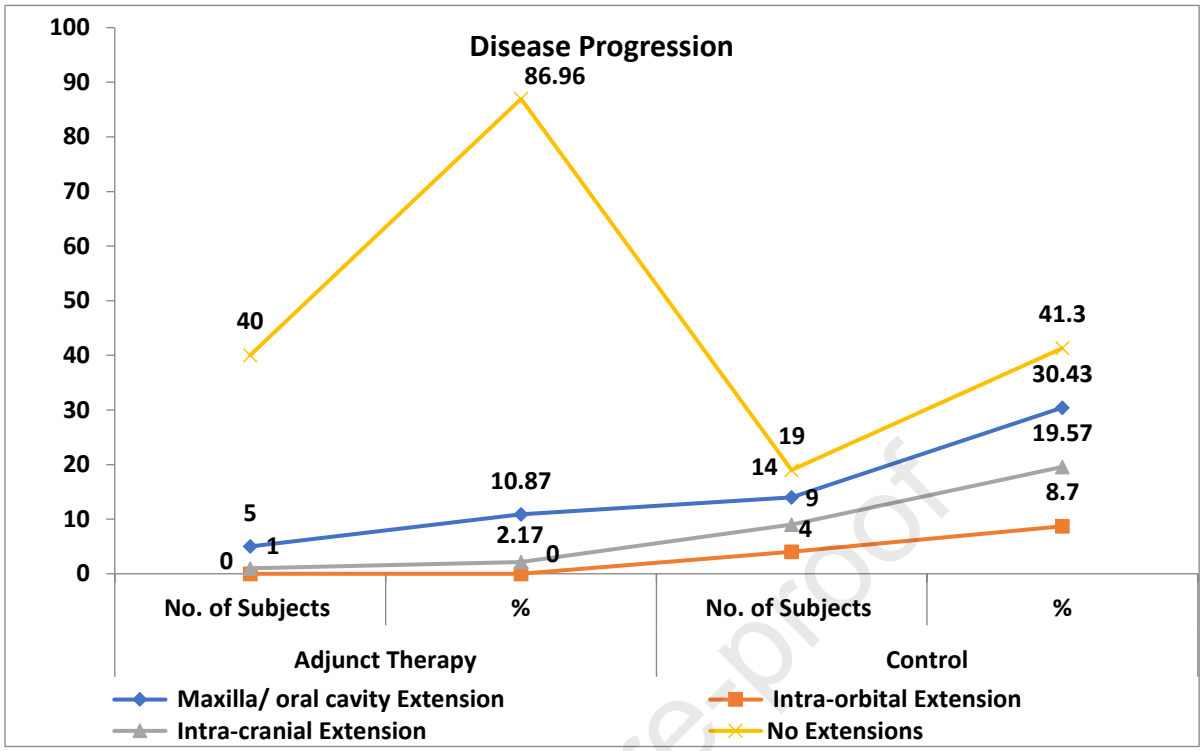


Figure 3: comparisons of the Disease progression in both groups

Table 5 : Comparisons of the need for additional surgical interventions between groups

Sl. No	Surgical intervention	Group A (AAT+CAT)		Group B (ACT)	
		No. of Subjects	%	No. of Subjects	%
1	Partial Maxillectomy	5	10.87	13	28.26
2	Complete Maxillectomy	0	0	1	2.17
3	Enucleation	0	0	4	8.7
4	No Any Surgical Intervention Required	41	89.13	28	60.87
Total		**46**	**100**	**46**	**100**

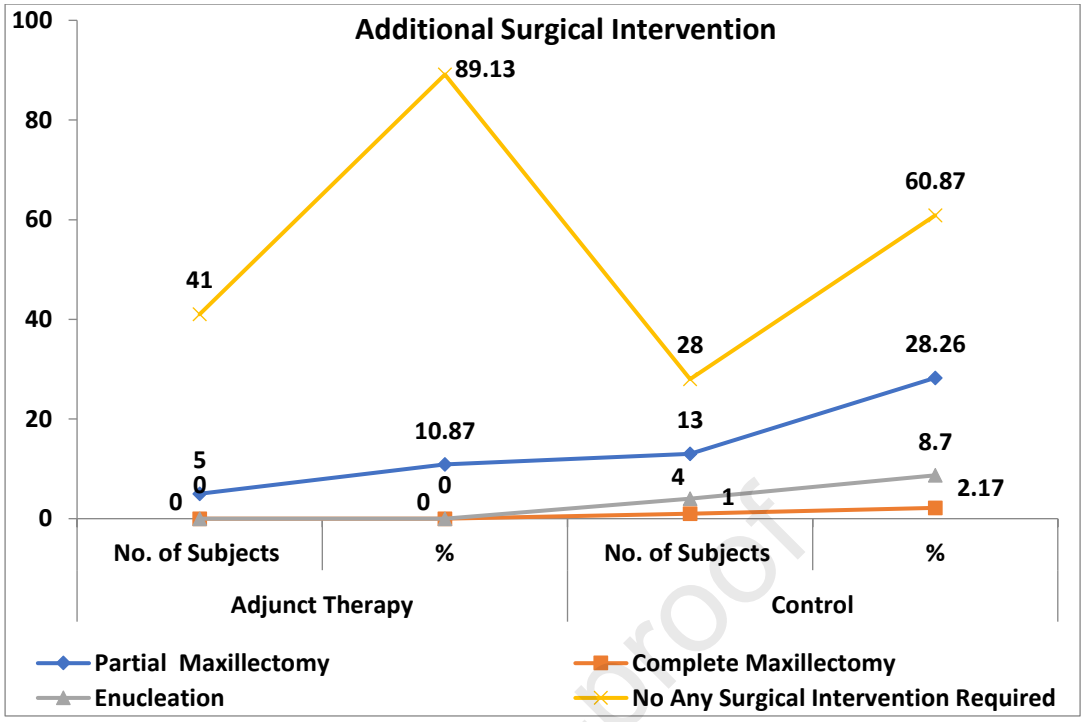


Figure 4: comparisons of the need for additional surgical interventions between groups

(v) **Mortality & Adverse effects**: There was no mortality in the 92 patients during the study period of 45 days and also for an extended observation period of three months in both adjunct therapy and control group. However, 2 patients from group A and 5 from group B have reported nausea, which could be due to use of oral Posaconazole. No other major adverse effects have been observed during the study.

(vi) **Bio-chemical parameters:** The safety of both arms of the therapy has been determined by liver function and renal profile which are with in normal range in both groups.

Discussion:

Ayurveda has long before identified the relation between the ailments of nose, oral cavity, eye, ear and brain, not just for their closer proximity but also due to their inter connectivity. Acharya Charaka mentioned nose as the gate way of brain by stating *"NasahiShirasodwaram",* which appears very true considering the spread of disease Mucormycosis from the channels and

sinuses of nose to brain. All the ailments related to nose, eye, ear and brain in Ayurveda are grouped under one single disease entity called *"Urdhwajatrugata-vyadhi"*, a word referring to ailments manifesting above the region of neck. [13,14,15]

Mucormycosis is an aggressive, rapidly progressive fungal ailment mimicking its symptomatology with some of *urdhwajatrugata*rogas (ailments of supraclavicular region) such as *Dusta-peenasa (sinusitis),* Mukha-rogas (diseases of oral cavity), *chaladanta(loosening of teeth),talu paka* (Palatal abcess), Netrabhishyanda(conjunctivitis), Akshipaka (*pan ophthalmitis),* Adhimantha (conditions similar to glaucoma) and Hatadhimantha(Atropic bulbi).

PCM most often begins at the channels of nose, with nasal block (pratisyaya) and pain as the first symptom. The upadrava/ complications of pratisyaya has been stated as Andhya (blindness), which is observed in patients of PCM in the form of loss of vision. Acharya Susruta denoted a clinical condition called *Akshipaka (pan ophthalmitis)* and *Adhimantha* in *drusti gata rogas*. It has been emphasised that the inflammatory condition of eye Akshipaka (*pan ophthalmitis),* if not managed properly may lead to an incurable stage called *Adhimantha,* leading to a vision loss. Considering all the above possibilities, AAT for the current study was designed. [15-18] Ayurvedic parameters related to PCM have been assessed in all patients as the following table. (Table no 5).

Table 5: Symptoms assessed in patients as per Ayurveda textual references [23}

Sl.No.	Symptoms related to Nose found in patients of mucormycosis
1	Singhnakam-ghanam (thick mucoid discharge)
2	Na vetthi-gandharasamcha (loss of smell and loss of taste)
3	Shushyathi- pinasa (dryness of the nose)
4	Ganda-akshi-shankha-rujam (pain in the eyes and temple region)

5	Pari shoshite (extreme dryness of the nose)
6	Kruchra-uchwasanam(difficulty in breathing)
7	Shookapurna-nasa(cruts)
	Symptoms related to oral cavity and teeth
1	Chaala-danta (Loosening of teeth)
2	Bhakshanani-Adhikavyadha(severe pain while eating)
3	Talu-mamsena-pitika(eruptions on the mucosa of palate)
4	Shwayathu(swelling of gums)
5	Ruja(pain)
6	Paka(suppuration)
7	Puya-sravi(discharging of pus)
8	Maharuja(severe pain)
	Symptoms of Eye
1	Akshi Sopha (Swelling of eye)
2	Gouravam (Heaviness of eye ball)
3	Stambhana(loss of movement/stiffness)
4	Shankha-akshi-bhru-lalata-toda-spurana,bhedanam(pain at frontal eye region)
5	Nimesha-unmesha-kruchrath(difficulty in opening and closing of the eyelids)
6	Gurutha(heaviness)
7	Akshishopha(swelling of the eye)
8	Nidra(sleepiness)
9	Annanabhilasham(dislike for food)
10	Netra utpatya(severe pain on eye ball)

Ayurveda intervention used in the present study included compound herbo mineral drugs namely, "*Gandhaka rasayana*", "*Kaisora guggulu*" based on their antifungal activity, "*Vasantakusumakar ras*", "*Nishamalaki*" considering their immune boosting effect, "*Dasamula katutrayadi Kashaya*" tablet and "*Vyoshadi vati*" for its potential to reduce severity of symptoms. Some of the local measures employed included, "*Surasadi gana taila*" in a dose of 2 drops in each nostril which has been observed to provide good symptomatic relief in terms of reduction in feeling of heaviness, numbness and pain in the nose. Many patients observed cleansing of channels of nose after instillation of "Surasadi gana taila" in the form of nasal drops. Combination of "*triphala*" and "daruharidya churna", in the form of herbal decoction has been found to be helpful in minimising foul smell of mouth, oral ulcers and toothache. Fumes inhaled from a herbal stick made up "*triphala*" and "*daru haridra*" known as "*Dhooma pana*" in the ayurvedic context also has been advised in all patients. The fumes generated by lighting the herbal stick, which are allowed to inhale from nose and exhaled from mouth for three times in succession for three occasions in a span of twenty four hours. [13,15,16,19]

Additionally, efforts were made to analyse the basic anti-fungal activity of the above Ayurveda intervention drugs and was tested by the method of Agar well diffusion with a standard antifungal medicine. The study showed that *Kaisora guggulu, Gandhaka rasayanam, Dashamula Katutrayadi kashayam, Trifala - Daruharidra powder* were exhibiting good anti-fungal activity against *Aspergillus niger*. *Dashamula Katutrayadi kashayam* was also effective against Candida albicans.

The treatment of mucormycosis (black fungus) in recent Ayurveda literature was described by Mohsina *et al*, and Karthik *et al*., which is in line with the treatment we offered in the group A.[9,10] Rastogi S *et al*, in a recent case report had employed a saline nasal irrigation to be a primary intervention in suspected rhino-orbito-cerebral mucormycosis helps improving the recovery, which is also in line with one of the treatments in AAT+CAT group. [11] Authors

successfully managed the PCM with ayurvedic saline nasal irrigation case and also suggested that Ayurvedic innate constitution (*prakriti*) may be much beneficial in *pitta* people as compared to *vata* or *kapha* dominant people. People having allergic inflammatory sinus disorders do not benefit much from saline nasal irrigation [11] The current study results have shown benefits Ayurveda treatments in PCM cases when used as an adjuvant. The evidence is in line with existing case Reports of COVID-19 associated Mucormycosis in in Ayurveda and Homeopathy.[20] This shows a wide scope of these treatments to be explored with gold standard drugs. We pre-tested the ayurvedic drugs under *invitro* laboratory settings, likewise an invitro investigation had reported that *Anu taila* was found effective against *Mucor* species. The authors concluded that repeated *nasal medication (oil)* application demonstrated rapidly abolished fungal microarchitectures than amphotericin B in scanning electron microscopy (SEM) images. In the present study "*surasadi gana taila"* (herbal medicated nasal drops) has provided instant symptomatic relief patients on AAT. This mechanism of action of this herbal nasal-drops is that they can suppresses mucormycosis by regulating host TNF-α response and inhibiting the fungal ergosterol biosynthesis. [21] The level of evidence comes from case reports/ invitro reports [11,20,21] in ayurvedic literature, whilst the current study adds valuable evidence from a clinical study with comparisons with conventional therapies. It difficult to contrast the exact observations from outcomes of the current study with the above existing evidence, as study designs are not the same (case reports *vs* original experimental study). The lessons learnt from loss of patients, underrated benefits of traditional Indian treatments during 2nd wave of COVID-19 are highlighted in recent literature, recommending further clinical studies. [22]

The merits of the study lie in the use of pre-tested Ayurveda therapy and the use AAT+CAT for PCM which is a novel addition to Ayurvedic medical literature. The limitations lie in short duration of follow up and non-random allocation while grouping. Mucormycosis as such needs an extended follow up for at least for period of six months to rule out the possibility relapse of

the disease. The future directions include larger clinical trials with the use of Ayurveda regimen used here in multicentric cohort studies to establish the direct efficacy of the stated regimen for PCM.

Conclusion: Adjunct Ayurveda with conventional allopathic intervention (AAT+CAT) for PCM showed a better cure measured in terms of symptom score, disease progression, need of conventional antifungal medicines and surgical requirements as compared to those who received conventional allopathic therapy (CAT) alone. The combination (AAT+CAT) is not only therapeutically effective, but also safe and economical option to consider for PCM. The study shows that antifungal efficacy and the role of Ayurveda in management of emergency state such as epidemics with outburst of contagious infections. Exploring the role of such ayurvedic therapeutic options may aid in saving lives in pandemic. The study could be witnessed as a step closer towards an integrated approaches in the healthcare sector in the near future.

Acknowledgements: We are highly indebted to the support we received from Commissioner Department of AYUSH, Dr. Alagu Varsini IAS, for the initiation and monitoring at of the study every stage. We also acknowledge and thank Dr.T.Shankar, Superintendent Government ENT Hospital Koti, Hyderabad and Dr.Manish Gupta, Associate Professor, ENT hospital, Hyderabad for providing facilities to work at Government ENT hospital, Hyderabad for conducting study. We thank Dr. V. Balakrishna, Drug inspector, Dept of Ayush, Telangana, Dr. Saketh ram, Research officer, NIIMH-CCRAS, Hyderabad. We convey our thanks to Dr. Ak. Sailaja. Head Dept of Pharmaceutics, RBVRR, women's college of pharmacy, Hyderabad for conduction of lab analysis of antifungal properties of Ayurveda intervention drugs. The contribution of the following PG scholars Department of Shalakya, BRKR Government

Ayurvedic college, Hyderabad, Dr. Paidipala Girija Shree, Dr.Mangilipally Divya, Dr.A. Mallikarjun, Dr. Nalini Yadav, Dr. Punnam ramya kumari is worth mentioning as they worked in the wards maintaining case records and follow-up studies of patients. Internees Dr Akshay Tandley, Dr.P. Mounika priyadarshini Dr.D.Anagha , Dr Hima vani ,Dr Himanshi Choudhary, Dr.P Pravalika yadhav and Dr Varthya mohan naik extended support in data collection. We Thank" *Dr Santosh Palla for redrafting manuscript/ critically reviewing as per journal guidelines* ."

Financial support: Entire financial support for the project has been extended by Department of AYUSH, Telangana. [Reference Letter no: 446/C/2021]

Conflict of interest; No conflict of interest is present with this study.

References

1. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. J Laryngol Otol. 2021;135(5):442-447.

2. Deaths due to black fungus in India https://www.tribuneindia.com/news/ludhiana/mucormycosis-cases-on-decline-in- punjab-289209. Available from: https://www.aa.com.tr/en/asia-pacific/india-reports-more-than-4-300-deaths-from- black-fungus-to-date/2310117

3. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, Puri GD, Chakrabarti A, Agarwal R. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. Mycopathologia. 2021;186(2):289-298.

4. Hyderabad Ayurvedic treatment for black fungus to start today .Acessed from https://timesofindia.indiatimes.com/city/hyderabad/ayurvedic-treatment-for-black-fungus-cases-to-start-today/articleshow/82956177.cms
5. Sood A, Nayyar V, Mishra D, Kakkar A, Priya H. Post-COVID mucormycosis: Ascertainment of the pathological diagnostic approach. J Oral Maxillofac Pathol. 2021;25(2):219
6. India reports 45,374 Black fungus cases, 4,332 deaths so far. Accessed from: https://telanganatoday.com/india-reports-45374-black-fungus-cases-4332-deaths-so-far
7. Pushparaj K, Kuchi Bhotla H, Arumugam VA, Pappusamy M, Easwaran M, Liu WC, Issara U, Rengasamy KRR, Meyyazhagan A, Balasubramanian B. Mucormycosis (black fungus) ensuing COVID-19 and comorbidity meets - Magnifying global pandemic grieve and catastrophe begins. Sci Total Environ. 2022 Jan 20;805:150355.
8. Rastogi S, Pandey DN, Singh RH. COVID-19 pandemic: A pragmatic plan for ayurveda intervention. J Ayurveda Integr Med. 2022;13(1):100312.
9. Mohsina FP, Faheem IP, Tabassum S, Shah I, Ahmad A. An insight of mucormycosis (black fungus) in ayurveda. Open Journal of Pharmacology and Pharmacotherapeutics. 2021;6(1):013-7.
10. Karthik KP, Dileep A, Rajagopala S, Mahapatra AK, Dharmarajan P. Ayurveda approach to mucormycosis and other fungal infections: A comprehensive review. Journal of Indian System of Medicine. 2021;9(4):216.
11. Rastogi S, Verma A. Jalaneti (saline nasal irrigation) as primary intervention in suspected rhino-orbito-cerebral mucormycosis helps improving the recovery: A case report. Journal of Ayurveda and Integrative Medicine. 2022;13(2):100516.

12. Prasanna Kumar T, Vijay Kumar G,YumnamDhanesori Devirajivgandhi university of health sciences: in-vitro antifungal activity of gandhakarasayana, 2010, (Gandhak Rasayana) Acessed from: https://www.ijam.co.in/index.php/ijam/article/view/23
13. Saokar RM, Sarashetti RS, Kanthi V, Savkar M, Nagthan CV, Screening of Antibacterial and Antifungal Activity of GndhakaRasayana – an Ayurvedic Formulation. International Journal of Recent Trends in Science and Technology, 2013; 8(2):134-137.
14. Gupta V , Bansal P , sahu M , sachdeva K , ghaiye P. An Ayurvedic Polyherbal Formulation Kaishore Guggulu: A Review. International Journal of Pharmaceutical & Biological Archives 2011; 2(1):497-503.
15. Lather A, Gupta V, Bansal P, Sahu M, Sachdeva K, Ghaiye P. An Ayurvedic polyherbal formulation Kaishore Guggulu: a review. Int J Pharm Biol Arch. 2011;2(1):497-503.
16. Lather A, Gupta V, Bansal P, Sahu M, Sachdeva K, Ghaiye P. An Ayurvedic polyherbal formulation Kaishore Guggulu: a review. Int J Pharm Biol Arch. 2011;2(1):497-503.
17. Deogade MS, Pandya T, Prasad KS, Gupta H. Surasadi Gana Dravya-A review. Journal of Indian System of Medicine. 2016;4(2):114.
18. Peterson CT, Denniston K, Chopra D. Therapeutic uses of triphala in ayurvedic medicine. The Journal of Alternative and Complementary Medicine. 2017;23(8):607-1
19. Goli D. Anti-diabetic activity of stem bark of Berberis aristata DC in alloxan induced diabetic rats (Doctoral dissertation, RGUHS).
20. Javed D, Dixit AK, Vats H, Anwar S, Giri N. Review of Published Case Reports of COVID-19 Associated Mucormycosis with Search of Therapeutic Potential in Ayurveda and Homeopathy.

21. Balkrishna A, Rastogi S, Kharayat B, Tomer M, Varshney Y, Singh K, Kumari P, Dev R, Srivastava J, Haldar S, Varshney A. Anu taila, an herbal nasal-drop, suppresses mucormycosis by regulating host TNF-α response and fungal ergosterol biosynthesis. Journal of applied microbiology. 2022 Jan 13.
22. Panda AK, Palei DT, Rout S, Kar S. Ayurveda approaches to COVID-19 in 2nd wave: Lessons learned from practice.
23. K.R. srikantha Murhty, Susruta Samhita, Vol 3, Uttara Stana, chapter 6 &22, Choukamba Orientalia, Varanasi

Conflict of Interest and Authorship Conformation Form

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