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Global Journal of Medical, Pharmaceutical, and Biomedical Update

Review Article

The double trouble: COVID-19 associated mucormycosis a focused review and future perspectives

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Received : 17 June 2021
Accepted : 19 June 2021
Published : 03 July 2021

DOI
10.25259/GJMPBU_4_2021

Quick Response Code:

ABSTRACT

Mucormycosis, a deadly fungal infection, has affected thousands of COVID-19 patients in India. Mucormycosis, formerly known as zygomycosis, is caused by the many fungi that belong to the family "Mucorales." These molds are commonly found in soil, air, and damp walls and frequently colonize oral mucosa, nose, paranasal sinuses, and throat. The pathophysiological consequences of diabetes combined with the acute inflammatory surge in COVID-19 and steroid treatment weakens person's immunity and renders susceptibility to fungal infections. Patients treated for severe COVID-19 have damaged lungs and suppressed immune system, an environment that supports fungal infection. Fungal spores can grow in airways or sinuses, and invade bodies' tissues, explaining why the nasal cavity and paranasal sinuses are the most common site of mucormycosis infection, the consequential spread to the eyes can cause blindness, or causing headaches or seizures if the infection spreads to the brain. Poorly controlled diabetes often results in acidosis in tissues a suitable environment for Mucorales fungi to grow, exacerbating the risk for mucormycosis. This becomes clinically important, especially in India that has an increased prevalence of undiagnosed and uncontrolled diabetes. Given that a significant increase in the cases of mucormycosis in the diabetic patients treated for COVID-19 is strongly associated with corticosteroid administration, there is a need to evaluate use of dietary nutraceuticals with immune boosting potentials that modulate metabolic abnormalities in the management of COVID-19 associated mucormycosis.

Keywords: Mucormycosis, Black fungus, COVID-19, Diabetes mellitus, Corticosteroid therapy, Immunosuppression, Nutraceuticals and immune modulators

INTRODUCTION

Mucormycosis, formerly known as zygomycosis, a disease caused by the many fungi that belong to the family "Mucorales." Fungi in this family are usually found in the environment – for example, in soil and are often associated with decaying organic material such as fruit and vegetables. The fungus that is often responsible for infections in humans is *Rhizopus oryzae*. However, the family *Apophysomyces* found in tropical and subtropical climates (as in India), are commonly identified as the infective agents. Although mucormycosis epidemiology has been challenging to study due to its low incidence and diagnostic limitations, cases have continued to rise in diverse populations.[1-6] Given that the immunocompromised patients with hematological diseases and patients with a metabolic syndrome characterized by diabetes mellitus (DM) are at particular risk of mucormycosis.

COVID-19 has raised a primary global concern of COVID-19 Associated Mucormycosis (CAM) outbreak.[7]

SARS-CoV-2 infection has rapidly spread worldwide, infected over 178,566,293 people, caused more than 3,865,904 deaths in 220 countries, and is still spreading at the time of manuscript preparation (worldometers.info).[8] So far, there is no definite line of the approved treatment for this disease except for the vaccines (based on the mRNA and adenovirus technology) that have been approved for emergency use and several candidate vaccines under investigation. Early in the outbreak, concerns have been raised regarding the use of non-steroidal anti-inflammatory drugs (NSAIDs) associated with an increased risk of adverse effects in COVID-19 patients. However, the WHO concluded no evidence of adverse events resulting from NSAIDs use in COVID-19 patients in April 2020.[9] Several antiviral drugs and immunotherapies have been evaluated and are under clinical trials. As of October 22, 2020, the antiviral drug Veklury (remdesivir) is the only drug fully approved for the treatment of COVID-19 in hospitalized adults and children of age 12 years and older who weigh at least 40 kg (fda.gov).[10] The FDA issued an emergency use authorization (EUA) for convalescent plasma on August 23, 2020 and the monoclonal antibodies (bamlanivimab plus etesevimab) as of April 2021 (www.fda.gov).[11,12] The FDA note stated that COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains anti-SARS-CoV-2 antibodies, and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications.[11] It is an investigational product and is not currently approved or licensed for any indication. The initial issuance of this EUA for COVID-19 convalescent plasma was based on review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the National Convalescent Plasma Expanded Access Protocol sponsored by the Mayo Clinic.[11] Systemic corticosteroids are indicated in patients with severe and critical COVID-19.[13,14]

In late May 2021, according to the articles published in the lay press – Business Standards,[15] Times of India,[16] the surge of the number of cases of mucormycosis (black fungus) in people recovering from COVID-19 led to the declaration of the black fungus an epidemic in four states in India by making it a notifiable disease under the Epidemic Diseases Act 1897.[16] Mucormycosis occurs most commonly in immunocompromised patients and patients with uncontrolled diabetes.[17,18] The patients with iron overload are also susceptible to mucormycosis.[19] Clinical evidence suggests that both mononuclear and polymorphonuclear phagocytes are the principal host defense mechanism against *Mucorales*.[1] The patients with neutropenia and dysfunctional phagocytes are at high risk of developing mucormycosis. Hyperglycemia and acidosis allow the proliferation of the fungus by impairing the chemotactic ability of phagocytes toward the organism.[20] Corticosteroid therapy also enhances the patient's susceptibility to mucormycosis by impairing the role of bronchoalveolar macrophages in preventing spore germination following nasal inoculation and causing functional defects in circulating neutrophils.[21]

ASSESSMENT OF THE CAM OUTBREAK

Based on the anatomical locations, mucormycosis can be divided into the following categories – rhino-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous.[1,2] The emerging case of mucormycosis in association with COVID-19 from the published studies has been reviewed with outcomes that will benchmark and provide an avenue for both treatment and management of the conditions.[22-26] Table 1 summarizes the characteristics of the mucormycosis cases. The studies show that the prevalence of mucormycosis is more in male patients compared to female patients.[22-26] Singh *et al.*,[22] in their systemic review on 101 cases of mucormycosis in COVID-19 patients, identified DM (83.3%) and corticosteroid therapy (76.3%) as the most common risk factors, and upper respiratory tract involvement (88.9%) as most common findings and reported the mortality in 30.7% cases. Similarly, John *et al.*,[23] reported a mortality rate of 48.7%. It was interesting that of all the cases of COVID-19 associated mucormycosis about 80.4–96.7% of the patients had the DM (mean HbA1C ~10) and 87.8% patients were on corticosteroid therapy.[22-24] Ravani *et al.*,[24] in their retrospective study, reported uncontrolled DM (97.7%), COVID-19 infection (61.2%), and corticosteroid use (61.2%) as significant risk factors, whereas pansinusitis (77.41%) and orbital cellulitis (61.29%) were common presentation. In addition, authors also reported the mortality rate of 9.78%. Sharma *et al.*,[25] in their study, reported 23 cases of mucormycosis. They found that all cases were related to COVID-19 and ethmoids were the most common affected sinus. There was an intra-orbital extension in 43.47% of cases and intracranial extension in 8.69% cases.[25] They also reported that the diabetes and steroids as risk factors. Interestingly, Pakdel *et al.*,[26] reported CAM cases during the first wave (April–September 2020) of the COVID-19 pandemic compared to most of the other studies. A case of gastrointestinal mucormycosis in an elderly patient of COVID-19, which is a rare disease but has a mortality up to 85% had been reported.[27] The reader is referred to the review of Singh *et al.* which articulates that those individuals with diabetes and obesity tend to develop more severe COVID-19 infections, and subsequent addition of corticosteroids will increase the risk of mucormycosis.[22] Caution regarding any conclusion is of the essence, given that there are currently no studies that compare patients of mucormycosis in non-diabetic COVID-19 who did not receive steroids versus COVID-19 patients who received

Table 1: Characteristics of the CAM cases.

Author	Singh *et al.*[22]	John *el al.*[23]	Ravani *et al.*[24]	Sharma *et al.*[25]	Pakdel *et al.*[26]
Type of study	Systematic review	Systematic review	Retrospective institutional cohort	Prospective observational study	Prospective descriptive study
Number of cases	101 cases	41 cases	31 cases	23 cases	15 cases
Country	82 cases – India 19 cases – Rest of the world	USA	India	India	Iran
COVID positivity	Active – 59.5% Recovered – 40.6%	Mild – 2.4% Severe – 31.7% Critical – 19.5% ICU – 36.5%	19 cases – 61.2%	Active – 17.4% Recovered – 82.6%	Mild – 13.3% Moderate – 26.6% Severe – 53.3%
Age/Age range	27–78 years	46–61 years	20–80 years	Not available	14–71 years
Gender	78.9% – Male 22.1% – Female	82.9% – Male 17.1% – Female	64.5% – Male 35.5% – Female	65.2% – Male 34.8% – Female	66% – Male 34% – Female
Comorbidity	83.3% – DM 14.9% – DKA 3% – Leukemia/ Lymphoma 1% – Heart transplant 13% – No comorbidity	80.4% – DM 19.5% – DKA 12.1% – Renal failure	96.7% – DM 54.8% – Hypertension 6.45% – Kidney disease 3.22% – Ischemic heart disease	52.17% – DM (Uncontrolled) 39.13% – DM (Controlled) 60.87% – Hypertension 4.34% – Renal failure	86% – DM 46% – Hypertension 13% – Hematological Malignancies 13% – Asthma 13% Cardiovascular disease 6% – DKA
Corticosteroids	76.3% – Yes	87.8% – Yes	61.2% – Yes	100% – Yes	46.6% – Yes
Location	88.9% – Nasal/Sinus 56.7% – Rhino-orbital 22.2% – Rhino-orbito-cerebral 14.9% – Bone involvement 6.5% – Pulmonary 1% – Gastrointestinal 1% – Cutaneous	7.3% – Sinusitis alone 2.4% – Rhino-orbital 26.8% – Rhino-orbital-cerebral 7.3% – Rhino-cerebral 7.3% – Pneumonia 9.7% – Others	77.41% – Pansinusitis 61.29% – Orbital cellulitis 22.58% – Intracranial extension	100% – Sinuses 43.47% – Intra-orbital 39.13% – Palate 8.69% – Intracranial	47% – Rhino Orbital 33% – Sino Orbital 13% – Orbital 7% – Sinus
Mortality	30.7%	48.7%	9.78%	Not available	46.6%

CAM: COVID-19 associated mucormycosis, NR: Not reported, DM: Diabetes mellitus, DKA: Diabetes ketoacidosis

steroids and developed mucormycosis.[22] It is not easy to establish a cause-and-effect relationship between SARS-CoV-2 infection, mucormycosis, and corticosteroids.[22]

PATHOPHYSIOLOGY AND MANAGEMENT OF CAM

COVID-19 can trigger mucormycosis by alterations in cell-mediated immunity, such as chemotaxis, phagocytosis, and cytokine secretion in susceptible patients.[28] Certain conditions such as uncontrolled DM with or without diabetic ketoacidosis, hematological malignancies, corticosteroid therapy, organ transplantation, prolonged neutropenia, immunosuppressive agents, and iron overload increase the patients' risk for developing mucormycosis.[29] Song *et al.*,[30] suspected the fungal co-infection association with global COVID-19 pandemic in a retrospective analysis, especially in severely ill or immunocompromised patients and provided a diagnostic/therapeutic pathway in the management of aspergillosis, candidiasis, mucormycosis, or cryptococcosis as co-morbidities in COVID-19 patients. Pandiar *et al.*,[31] asserted that SARS-CoV-2 crafts a suitable microenvironment for opportunistic infections like mucormycosis by dysregulation of Angiotensin-Converting Enzyme-2 (ACE-2) expression not only in lungs but also in esophagus, pancreas, ileum, colon, cardiovascular, and renal tissues. COVID -19 produces an acute diabetic like state due to its effects on ACE-2 in the pancreatic beta cells and produces hyperglycemia.[32,33] Lactic acidosis due to damage to type II alveolar cells causing the cell to convert to anaerobic glycolysis, which is a known risk factor for mucormycosis. Dysregulation of ACE-2 in the vascular endothelium leads to endothelial damage and vascular thrombosis. Many ICU-related vascular interventional

procedures (like central venous access) and ventilatory support can also lead to vascular endothelial injury and venous stasis. An elevated serum ferritin and serum iron level due to hemolysis and acidosis, respectively, provides a source of nutrition to *Mucorales*.[34] Lymphopenia is also a feature of COVID-19 infection.[32,35] In addition, *R. oryzae* is a fast-growing organism at 3 mm/h at 36°C that allows mucor to grow first when optimal conditions are met.[31,36] Mucor species are thermotolerant and can efficiently survive the raised temperature associated with COVID-19 infection.[31] No similar mucor outbreaks in immunocompromised patient populations, like those with diabetes, cancer, receiving chemotherapy, and steroids, prompt toward the unique cascade triggered during COVID-19 as the likely causative for CAM. Similarly, the hypothesis of the use of industrial oxygen as the trigger for mucormycosis outbreak seems weak, as causative fungi are ubiquitous so may not be directly affected by additional carrier like oxygen. In addition, mucor cases recorded in patients without oxygen use further bolsters alternate reasoning for the outbreak rather than the industrial oxygen usage. Overall, from the above observations, we believe that COVID-19 itself produces immunosuppression, insulin resistance, and an independent risk factor for mucormycosis.

Direct microscopy, histopathology using H and E staining and culture are the cornerstones of diagnosis.[37] Mucormycosis is suspected on direct microscopic examination of clinical specimens such as sputum, paranasal sinus secretions, bronchoalveolar lavage and skin lesions, preferably using optical brighteners. The fungi are characterized by broad and non-septate hyphae. The culture of a specimen is strongly recommended to confirm the diagnosis. High-dose liposomal amphotericin B is the first line of drug, while new oral antifungal posaconazole is recommended for step-down or salvage therapy after initial amphotericin B treatment.[38] Delaying amphotericin B therapy increases mortality significantly.[39,40] Prompt surgical debridement remains the cornerstone for better survival outcomes.[38-40]

A few studies have suggested the role of nutraceuticals in the treatment of COVID-19. The natural compounds andrographolide, berberine, curcumin, mangiferin, nimbin, piperine, theaflavin, withaferin A, gallic acid, luteolin, naringenin, quercetin, resveratrol, and zingiberene exhibited a binding affinity for the ACE-2 receptors and inhibit the attachment of the SARS-CoV-2 virus to the host cell.[41,42] The anti-inflammatory properties of the spices can be exploited to reduce the cytokine storm in COVID-19 patients.[42,43] Diet may have the ability to mitigate inflammation, and nutraceuticals may become accountable to inhibit viral entry. The role of dietary nutraceuticals can be evaluated as an additional measure in the management of CAM.

CONCLUSION

Mucormycosis is an invasive opportunistic infection leading to rhino-orbito-cerebral infection as the most common presentation. Studies show a rising trend of the life-threatening CAM in affected and recovered patients globally and more so in India. A significant increase in the CAM cases is strongly associated with systemic corticosteroid administration in the diabetic patients treated for COVID-19. SARS-CoV-2 directly triggering immunosuppression, insulin resistance through the cytokine cascade should be explored as an independent risk factor for CAM. Whenever mucormycosis is suspected, due to rapid progression and angioinvasive nature, swift diagnosis and treatment should be initiated. Hence, a high index of suspicion, early diagnosis, tight glycemic control, and elimination of steroid use are recommended. Prompt radical surgical debridement, liposomal amphotericin B, and posaconazole are the standard of care as of now. The role of dietary nutraceutical can be evaluated as a supplemental measure.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Spellberg B, Edwards J Jr., Ibrahim A. Novel perspectives on mucormycosis: Pathophysiology, presentation, and management. Clin Microbiol Rev 2005;18:556-69.
2. Brunet K, Rammaert B. Murcomycosis treatment: Recommendations, latest advances and perspectives. J Myco Medi 2020;30:1011007.
3. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, Chen SC. The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports. Clin Microbiol Infect 2019;25:26-34.
4. Jeong W, Keighley C, Wolfe R, Lee WL, Slavine MA, Chen SC, *et al*. Contemporary management and clinical outcomes of mucormycosis: A systematic review and meta-analysis of case reports. Int J Antimicrob Agent 2019;53:589-97.
5. Ibrahim AS, Kontoyiannis DP. Update on mucormycosis pathogenesis. Curr Opin Infect Dis 2013;26:508-15.
6. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clin Infect Dis 2021;54 Suppl 1:S16-22.
7. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM,

Arastehfar A, Gangneux J, *et al*. The Emergence of COVID-19 Associated Mucormycosis: Analysis of Cases from 18 Countries; 2021. Available from: https://www.papers.ssrn.com/sol3/papers.cfm?abstract_id=3844587. [Last accessed on 2021 Jun 18].
8. Coronavirus Cases. Available from: https://www.worldometers.info/coronavirus/?fbclid=IwAR35ZFiRZJ8tyBCwazX2N-k7yJjZOLDQiZSA_MsJAfdK74s8f2a_Dgx4iVk. [Last accessed on 2021 Jun 18].
9. The Use of Non-steroidal Anti-inflammatory Drugs (NSAIDs) in Patients with COVID-19. Available from: https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19. [Last accessed on 2021 Jun 18].
10. FDA Approves First Treatment for COVID-19. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19. [Last accessed on 2021 Jun 18].
11. Convalescent Plasma. Available from: https://www.fda.gov/media/141477/download. [Last accessed on 2021 Jun 18].
12. Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. Available from: https://www.fda.gov/media/145802/download. [Last accessed 2021 Jun 10].
13. World Health Organization. Therapeutics and Covid 19: Living Guideline. Geneva: World Health Organization; 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021. [Last accessed 2021 Jun 10].
14. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, *et al*. Early short-course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis 2020;71:2114-20.
15. Business Standard. India Reports 8,848 Mucormycosis Cases, More Amphotericin Vials Allocated. Available from: https://www.business-standard.com/article/current-affairs/india-reports-8-848-mucormycosis-cases-more-amphotericin-vials-allocated-121052200583_1.html. [Last accessed on 2021 Jun 09].
16. Times of India. Black Fungus Declared an Epidemic in 4 States, 1 UT. Available from: http://www.timesofindia.indiatimes.com/articleshow/82804720.cms?utm_source=contentofinterest and utm_medium=text and utm_campaign=cppst. [Last accessed on 2021 Jun 09].
17. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev 2000;13:236-301.
18. Danion F, Aguilar C, Catherinot E, Alanio A, DeWolf S, Lortholary O, *et al*. Mucormycosis: New developments into a persistently devastating infection. Semin Respir Crit Care Med 2015;36:692-705.
19. Ibrahim AS, Spellberg B, Edwards J Jr. Iron acquisition: A novel perspective on mucormycosis pathogenesis and treatment. Curr Opin Infect Dis 2008;21:620-5.
20. Baldin C, Ibrahim AS Molecular mechanisms of mucormycosis the bitter and the sweet. PLoS Pathog 2017;13:e1006408.
21. Chinn RY, Diamond RD. Generation of chemotactic factors by *Rhizopus oryzae* in the presence and absence of serum: relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis. Infect Immun 1982;38:1123-9.
22. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021;2021:19.
23. John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: The perfect storm for mucormycosis. J Fungi (Basel) 2021;7:298.
24. Ravani SA, Agrawal GA, Leuva PA, Modi PH, Amin KD. Rise of the phoenix: Mucormycosis in COVID-19 times. Indian J Ophthalmol 2021;69:1563-8.
25. 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;135:442-7.
26. Pakdel F, Ahmadikia K, Salehi M, Tabari A, Jafari R, Mehrparvar G, *et al*. Mucormycosis in patients with COVID-19: A cross-sectional descriptive multicenter study from Iran. Mycoses 2021;2021:13334.
27. Monte ES Jr., Santos ME, Ribeiro IB, Luz GO, Baba ER, Hirsch BS, *et al*. Rare and fatal gastrointestinal mucormycosis (Zygomycosis) in a COVID-19 patient: A case report. Clin Endosc 2020;53:746-9.
28. Revannavar SM, Supriya PS, Samaga L, Vineeth VK. COVID-19 triggering mucormycosis in a susceptible patient: A new phenomenon in the developing world? BMJ Case Rep 2021;14:e241663.
29. Sugar AM. Mucormycosis. Clin Infect Dis 1992;14:S126-9.
30. Song G, Liang G, Liu W. Fungal co-infections associated with global COVID-19 pandemic: A clinical and diagnostic perspective from China. Mycopathologia 2020;185:599-606.
31. Pandiar D, Kumar NS, Anand R, Kamboj M, Narwal A, Shameena PM. Does COVID 19 generate a milieu for propagation of mucormycosis? Med Hypotheses 2021;152:110613.
32. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23:623-62.
33. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47:193-9.
34. Xu H, Zhong L, Deng J. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12:8.
35. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-43.
36. Dijksterhuis J, Zygomycetes SR. Food Spoilage Microorganisms. Boca Raton, FL: CRC Press; 2006. p. 415-36.
37. Skiada A, Lass-Floerl C, Klimko N, Ibrahim A, Roilides E, Petrikkos G. Challenges in the diagnosis and treatment of mucormycosis. Med Mycol 2018;56 Suppl 1:93-101.
38. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SC, Dannaoui E, Hochhegger B, *et al*. Global guideline for the diagnosis and management of mucormycosis: An initiative of the European confederation of medical mycology in cooperation with the mycoses study group education and research consortium. Lancet Infect Dis 2019;19:e405-21.
39. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases

mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis 2008;47:503-9.
40. Ally MT, Jenkins IH, Gupta V. Mucormycosis: More than meets the eye! Am J Med 2019;132:1044-6.
41. Maurya VK, Kumar S, Prasad AK, Bhatt ML, Saxena SK. Structure-based drug designing for potential antiviral activity of selected natural products from Ayurveda against SARS-CoV-2 spike glycoprotein and its cellular receptor. Virusdisease 2020;31:179-93.
42. Kunnumakkara AB, Rana V, Parama D, Banik K, Girisa S, Sahu H, *et al*. COVID-19, cytokines, inflammation, and spices: How are they related? Life Sci 2021;2021:119201.

How to cite this article: Agnihotri AK, Vij M, Aruoma OI, Yagnik VD, Bahorun T, Villamil ME, *et al*. The Double Trouble: COVID-19 Associated Mucormycosis a Focused Review and Future Perspectives. Glob J Med Pharm Biomed Update 2021;16:4.