ORIGINAL RESEARCH

Differential Effects of Zinc and Iron on Rhizopus Oryzae and the Fungicidal Efficacy of Indian Spices extracts

Kavitha Bottu[1], Sindhu Subramani[1], Eileen Mary[1], Ramya Sekar[2]

Abstract

Introduction: During the second wave of the COVID-19 pandemic in India, a surge in mucormycosis cases occurred, primarily caused by Mucorales species such as Rhizopus oryzae (R. oryzae). It disproportionately affected individuals with compromised immune systems. In the therapeutic landscape of COVID-19 management, zinc and iron supplements were administered to support immune function. However, a widespread misconception emerged during this period, hypothesizing that zinc supplements and iron could facilitate the replication and proliferation of Mucor organisms. These findings underscore the need to critically evaluate micronutrient roles in infectious diseases and necessitate the exploration of alternative, evidence-based interventions of indigenous spices. In this context, the antifungal properties of traditional spices, such as cinnamon, clove, turmeric and black pepper, which are commonly used in Indian medicine, were evaluated in this study.

Methodology: The R. oryzae organism was cultured in vitro and its growth potential was assessed on iron and zinc supplementation. Further, the anti-fungal activity of ethanolic and methanolic extracts of the above-mentioned spices in different concentrations was assessed via the agar well diffusion method. Zones of inhibition were measured, and statistical analyses were performed using SPSS software. P-values < 0.001 were considered statistically significant.

Results: Iron supplementation significantly enhanced the growth of R. oryzae ($p < 0.001$), whereas zinc did not facilitate the growth of R. oryzae. Cinnamon exhibited superior antifungal efficacy in ethanol extracts, whereas clove showed enhanced activity in methanol extracts. The inhibitory effects of pepper and turmeric were less significant.

Conclusion: Iron supplementation promotes Rhizopus oryzae growth, zinc does not facilitate growth. Traditional spices, such as cinnamon and cloves, exhibit significant antifungal potential. Further Minimum Inhibitory Concentration (MIC) and in vivo investigations are needed to harness their role.

Keywords: Rhizopus oryzae, Cinnamon, Clove, Mucormycosis, Antifungal activity, Micronutrients, Ethanolic extracts, Methanolic extracts.

Introduction

The global pandemic of SARS-CoV-2 infection emerged in 2019 and affected many countries, including India. During the second wave of the COVID-19 pandemic in India, which commenced in March 2021, there was a substantial increase in both incidence and mortality rates.[1] Globally, as of September 2021, 230,953,959 patients were infected, and approximately 4,734,427 deaths were reported due to COVID-19. The total number of infected cases and mortality rates in India are 33,697,581 and 447,373, respectively.[2] During the second wave of COVID-19, the incidence of mucormycosis increased significantly in India. The Indian government reported 45,274 cases of COVID-19-associated mucormycosis (CAM), with 4332 associated deaths.[3] Individuals at greater risk of contracting CAM include diabetic ketoacidosis (DKA), those receiving steroid therapy, individuals with malnutrition, neutropenia, and other immunosuppressive conditions. Other possible causes include the use of industrial oxygen rather than medical oxygen in patients; a deficit of cleanliness in overwhelmed medical facilities; and the use of unclean masks, ventilators, and a lack of oxygen equipment.4 It was widely discussed within the medical community, zinc supplementation, which is administered as part of COVID-19 management, may have contributed to the proliferation of Mucorales, leading to COVID-19-associated mucormycosis.[3]

Department and Institution Affiliation: [1]Department of Oral & Maxillofacial Pathology and Oral Microbiology, Meenakshi Ammal Dental College and Hospital, Meenakshi Academy of Higher Education and Research (Deemed to be University), Chennai, Tamil Nadu, India; [2]Department of Oral Pathology & Microbiology, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India.

Corresponding Author: Dr. Sindhu Subramani, Assistant Professor, Department of Oral & Maxillofacial Pathology and Oral Microbiology, Meenakshi Ammal Dental College and Hospital, Meenakshi Academy of Higher Education and Research (Deemed to be University), Chennai -600095, Tamil Nadu, India. drsindhu.oralpathology@madch.edu.in

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Mucormycosis is the most common opportunistic fungal infection, apart from Candidiasis and Aspergillosis. Mucor infection caused by filamentous molds could be due to the inhalation of spores into the respiratory tract, ingestion of contaminated foods, or inoculation through the skin and mucous membrane.[5,6] Mucormycosis is caused by a fungus belonging to the class Zygomycetes in the order Mucorales. The taxonomy of Mucorales has evolved, with a total of 11 genera and 27 species described as causative agents. Genera such as Rhizopus (R. oryzae, R. microsporus, R. homothallicus, R. asexualis, R. stolinifier), Mucor (M. circinelloides), Lichtheimia (L. corymbifera, L. ramosa), Rhizomucor (R. pusillus), Cunninghamella (C. bertholletiae), Saksenaea (S. vasiformis, S. erythrospora) and Apophysomyces (A. elegans, A. variabilis) are known to cause mucormycosis. Among these, Rhizopus oryzae (R. oryzae) is the most common species associated with mucormycosis globally (50-60%).[7,8]

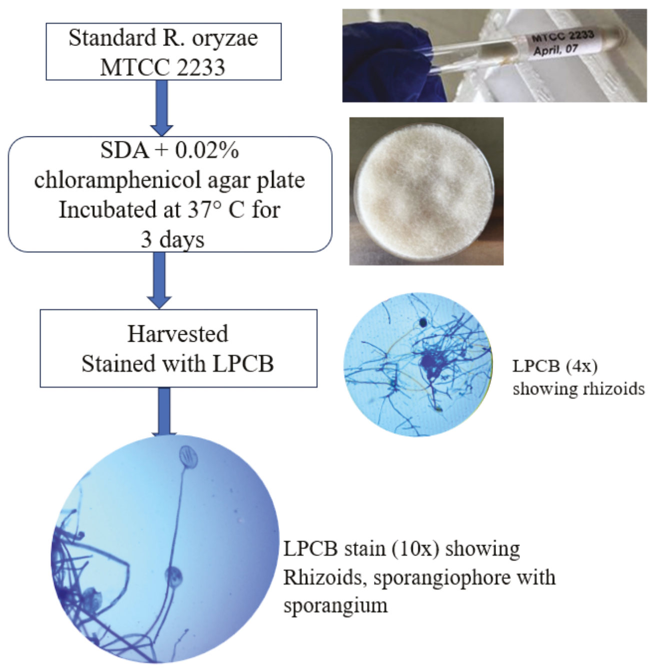

Fig. 1: Steps for cultivating an organism

The government of India (GoI) established an interdisciplinary AYUSH research and development task and guidelines for AYUSH clinical studies in COVID-19 to promote research and the creation of evidence regarding the effects of various traditional drugs on COVID-19.[9] India, known as the 'land of spices', is enriched with a history of natural plant products being used in herbal medicine for many decades.[10] Hence, this study was carried out to identify the potential influence of micronutrients (zinc and iron) on the growth of R. oryzae and to assess the antifungal effects of indigenous spices such as cinnamon (Cinnamomum zylancium), pepper (Piper nigrum), clove (Eugenia caryophyllus), and turmeric (Curcuma longa).

Materials and Methods

This is in- vitro study was carried out after obtaining approval from the Institutional Ethical Committee (MADC/IEC/II/64/2023).

Microorganism

The standard R. oryzae strain (MTCC 2233) was procured from the Microbial Type Culture Collection and Gene Bank.

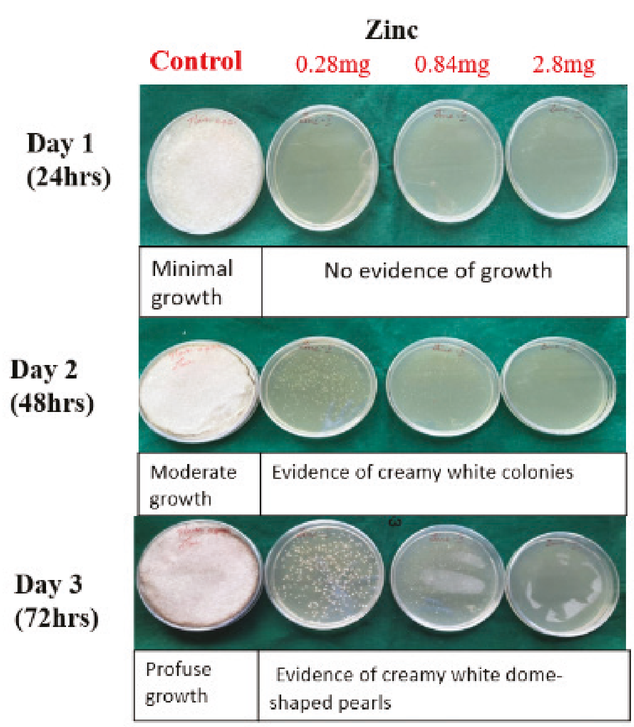

Fig. 2: Zinc-supplemented SDA agar plates with the morphology of growth of organism on the consecutive 24, 48 & 72 hrs.

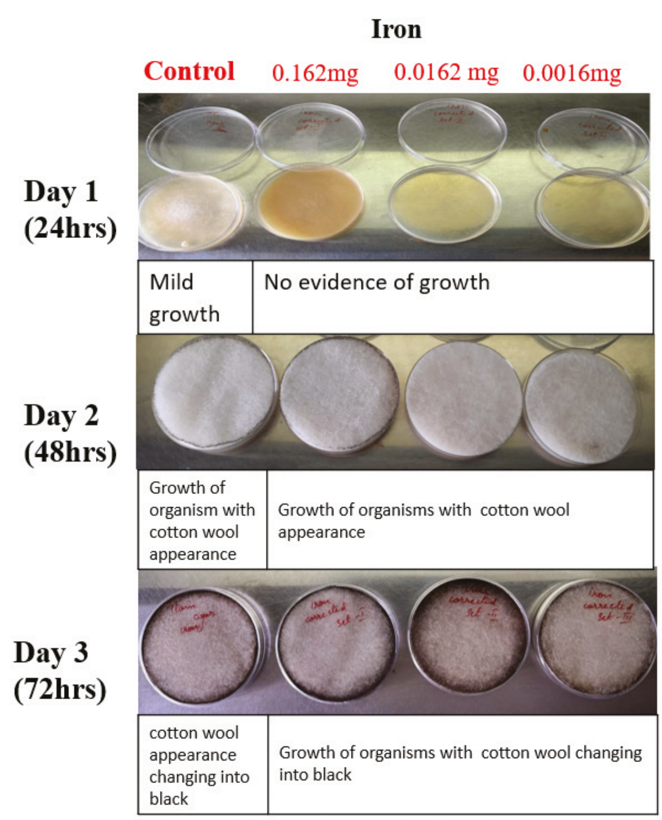

Fig. 3: Iron-supplemented SDA agar plates with the morphology of growth of organism on the consecutive 24, 48 & 72 hrs.

The strain was cultured on Sabouraud dextrose agar (SDA) with 0.02% chloramphenicol agar plate and incubated at 37°C for 5 days. The organisms were harvested and washed in phosphate-buffered saline (1x PBS) and stained with lactophenol cotton blue (LPCB).[5] The microscopic features of R. oryzae favor rhizoids with broad non-septate hyphae, and sporangia with sporangiospores were identified (Fig.1).

Figure 1

Enriched media

Zinc sulphate heptahydrate (ZnSo4.7H2O), Mol.wt. - 287.6 g/mol, was used as a source of zinc ions. The zinc content of 0.63 mg/L (1×10-5 M) is similar to the normal range of serum zinc. Three different zinc concentrations [0.28 mg; (1x10-5 M) equal to the normal range, 0.84 mg; (3x10-5M) higher than the normal range and 2.8 mg; (1x10-4 M) lower than the normal range] were used to evaluate the growth-potentiating impact of R. oryzae and zinc interaction.[5]

Ferric chloride, Mol.wt-162.2 g/mol, is used as a source for iron, and three different concentrations (0.162 mg(101), 0.0162; (10-1), 0.0016 mg; (10-2)) were calculated, similar to zinc, on the basis of its molecular weight and normal range. SDA agar without enriched media was used as a negative control, and the experiments were performed in triplicate.[5]

Inoculum preparation:

The sporangia were harvested via a sterile L-glass rod and washed in sterile phosphate-buffered saline (1x PBS). The inoculum of 103 sporangiospores/mL was adjusted with a hemocytometer. A 20 µl inoculum containing 103 spores/mL of each isolate were spread on SDA agar plates comprising the test and negative control and incubated at 37°C and observed for 24,48,72 hrs and the results were recorded.[5]

SPICES EXTRACT

Pre-Extraction Preparation

To ensure standardization, all spices such as Cinnamon, clove, pepper and turmeric of 100g each were procured from the same local market batch to ensure consistent geographic origin, cleaned thoroughly to remove dirt, air-dried under controlled room temperature, and ground into fine powder. The powdered samples were passed through a standardized sieve to obtain a uniform particle size before extraction

Extract preparation

Solvents were prepared with methanol and ethanol via the maceration technique; a fixed spice-to-solvent ratio (1:10 w/v) was maintained for all samples, i.e., 10g of ground spices were added to 100 ml of methanol and ethanol in a conical flask and kept in a shaking incubator for 24 hours at 100 RPM, and filtered with Whatman filter paper No. 1 at room temperature for complete solvent evaporation. The crude extracts were diluted to 100%, 50%, 25%, 12.5% and 6.25% with the inert solvent dimethyl sulfoxide (DMSO) as a negative control and posaconazole as a positive control.[10]

Statistical analysis:

The data collected from the study samples were tabulated in Microsoft Excel and subjected to statistical analysis. Statistical analysis was performed via SPSS software V26.0. The collected data were initially checked for normality and were normally distributed. The test of normality was performed via the Shapiro–Wilk test. Following the test of normality, the data for two-group comparisons were compared via an independent t-test (comparison between ethanol and methanol concentrations in different species). For more than 3 groups, the groups were subjected to one-way ANOVA (comparison of each spice at five different concentrations).

Table 1: Zones of inhibition of cinnamon, clove, pepper and turmeric in ethanol and methanol solvents at different concentrations (100%, 50%, 25%, 12.5% and 6.25%).

Spices	Ethanol					Methanol				
	100%	50%	25%	12.5%	6.25%	100%	50%	25%	12.5%	6.25%
Cinnamon	38 mm	28 mm	19 mm	15 mm	10 mm	33mm	19 mm	17 mm	13 mm	10 mm
Clove	34 mm	28 mm	26 mm	15 mm	12 mm	31mm	24 mm	20 mm	17 mm	15 mm
Pepper	22 mm	20 mm	18 mm	13 mm	10 mm	30mm	28 mm	23 mm	17 mm	12 mm
Turmeric	24 mm	18 mm	15 mm	14 mm	12 mm	22mm	20 mm	15 mm	13 mm	12 mm

Table 2. p values of four spice extracts in ethanol and methanol solvents at different concentration gradients

Spices	Ethanol					Methanol				
	100%	50%	25%	12.5%	6.25%	100%	50%	25%	12.5%	6.25%
Cinnamon	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Clove	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Pepper	0.006	0.006	0.006	0.006	0.006	0.001	0.001	0.001	0.001	0.001
Turmeric	0.009	0.011	0.010	0.010	0.010	0.001	0.001	0.001	0.001	0.001

- One-way ANOVA analysis ($p<0.001$)

Results

Zinc-enriched SDA agar media: Visual assessment of zinc-supplemented SDA agar plates on observations for 24, 48 and 72 h revealed creamy white dome-shaped pearls like colonies; the control plates presented a cottony wool appearance. (Fig. 2)

Iron enriched SDA agar media:

In iron-enriched media, the colonies were initially white (24 and 48 h), which later changed to black (72 h), similar to the control plates. (Fig. 3)

Spice extraction:

All four spice extracts evaluated with ethanol and methanol at four different concentrations presented variable degrees of inhibition zones against R. oryzae.

Table 1

Antifungal activity of various spice extracts (Cinnamon, Clove, Pepper, Turmeric) prepared in ethanol and methanol at different concentrations (100%, 50%, 25%, 12.5%, and 6.25%) is indicated by the diameter of the inhibition zones (in mm) measured against fungal growth. Cinnamon and clove had the greatest antifungal effects, particularly at the 100% concentration. (Table 1).

Table 2

On comparing the antifungal effect of spices in ethanol and methanol solvents at different concentrations, only cinnamon and clove extracts in ethanol solvent show significant antifungal activity (p value 0.001), whereas, all the four spices in methanol solvent show significant antifungal activity. (p value 0.001). (Table 2)

Discussion

Fungal infections are rare in healthy individuals, but the populations at risk are those with uncontrolled diabetes, steroid users, malnutrition, and other immunosuppressed conditions that act as predisposing factors. Among fungal infections, Candida was highly prevalent, but after the COVID-19 epidemic, there was upsurge in the incidence of Mucormycosis. Mucormycosis is common among individuals with uncontrolled diabetes and severe immunosuppression. According to a recent study, the prevalence of mucormycosis is estimated to range from 0.005 to 1.7 per million people worldwide (2019-2022). However, in India, the prevalence of mucormycosis is over 80 times higher (0.14 per 1000) than that reported in developed countries.[11] A multicenter study conducted in India reported a prevalence rate ranging from 1.8% to 3.36%, with the majority of affected patients being male (77%), whereas females constituted 23% of the cases.[12] Notably, the Rhino-orbitocerebral mucormycosis type is the most prevalent form of mucormycosis in India.[13]

In our study, zinc did not facilitate the growth of R. oryzae on SDA agar media at three different concentrations over periods of 24, 48, and 72 hours compared with the control. Notably, increasing the zinc concentration resulted in a reduction in colony number. In contrast, iron markedly enhanced R. oryzae growth, with increasing iron concentrations promoting profuse fungal proliferation.

According to the literature, fungi such as Aspergillus and Candida exhibit enhanced growth in the presence of zinc supplements.[14] However, in our study, zinc was found to suppress the growth of R. oryzae, one of the causative organisms of mucormycosis. Natural metals occur in various forms, including salts, sulfates, oxides, and nanoparticles. Fungi typically utilize metal ions following dissociation, allowing unbound ions to be effectively absorbed and transported within fungal cells. This discrepancy suggests that the suppressive effects of zinc on R. oryzae may be influenced by factors such as metal form, concentration, and fungal species-specific metal ion uptake mechanisms. Zinc ions hinder hyphal growth by increasing chitin deposition within the cell wall, which prevents hyphal extension but also increases hyphal branching and apical swelling, resulting in atypical hyphal morphology. Whereas in yeast cell morphology, zinc directly interacts with the nucleus which induces reactive oxygen species (ROS) formation causing cellular leakage, polarization and increases membrane potential with reduced cell wall integrity that leads to deprivation of fungi.[15]

In our study, iron supplemented Mucor growth. In contrast, iron chelators reduce the growth of fungal infections.[16,17] Iron is transported across the cell membrane through the copper oxidase-iron permease complex (FTR1), while intracellular iron is liberated from heme via heme oxygenase, thereby providing a substrate essential for fungal metabolism. Numerous studies have demonstrated that iron availability is a critical factor that enhances the growth and pathogenicity of mucormycosis. Under physiological conditions, transferrin sequesters iron, thereby restricting its availability to fungi, a mechanism known as nutritional immunity. However, during acidotic states such as diabetic ketoacidosis (DKA), the iron-binding capacity of transferrin is significantly diminished, resulting in increased free iron accessible to R. oryzae. Elevated iron levels promote fungal growth and virulence, particularly under conditions of iron overload or deferoxamine therapy. Therefore, iron homeostasis is a key determinant of a host's susceptibility to mucormycosis.[18]

Phytocompounds from plants and spices have been widely used in pharmaceuticals, natural therapies and food preservation since ancient times. Thus, scientific research into bioactive compounds widely used in traditional medicine, and these compounds are necessary adjuvant therapeutic compounds in healthcare.[19] Studies has gained utmost significance. However, the antifungal effectiveness of spice extracts are scarce. The methanolic and ethanolic solvent extracts of our native cinnamon, clove, pepper and turmeric against R. oryzae were analyzed in our work to evaluate their antifungal activity against different concentrations across various time periods (24, 48 and 72 hrs).

Among the four spices, cinnamon showed excellent antifungal properties against R. oryzae. Cinnamaldehyde reduces the activity of amino acid decarboxylase, thereby contributing to its antifungal properties. Fifty percent of the mixture contains cinnamaldehyde, a highly electronegative substance that disrupts biological processes requiring electron transport and combines with chemicals containing nitrogen to prevent microbes from growing. Our study findings concur with the research carried out by Khan et al., 2009 and Aneja et al., 2009.[20,21]

Second, our analysis revealed that the clove extract has antifungal activity, possibly because the eugenol present in the clove and most of the phenols and aldehydes present in the clove are thought to cause secondary membrane damage, which would increase their antifungal activity.[17] The black pepper exhibited an antifungal effect against R. oryzae, which can be attributed to the volatile oils of Pepper. It has been demonstrated to possess antibacterial properties, which could be the cause of the observed antifungal activity.[22,23] Turmeric is not as effective as cinnamon; the antifungal effect of turmeric may also be critically dependent on changes in membrane-associated ATPase activity and a decrease in proteinase secretion.[24,25] Thus, our study revealed that the cinnamon and clove extracts demonstrated the most effective antifungal activity in ethanolic and methanolic solvents (p value 0.001), with Cinnamon being marginally more effective in ethanol and clove in methanol. Numerous micronutrients and bioactive chemicals can be found in complex herbs and spices. Therefore, the use of the suggested herb–spice mixture may have various effects, including antiviral, antihyperglycemic, antifungal, anti-inflammatory, antioxidant and immunomodulatory effects, to reverse immune and metabolic changes in post-COVID-19 patients.[26]

Indian spices contain a wide range of bioactive phytochemicals with potent antifungal properties. Among these, flavonoids, phenolic compounds, alkaloids, tannins, terpenoids, and essential oils are the primary constituents responsible for antifungal activity. Cinnamon contains cinnamaldehyde, eugenol, and cinnamic acid, which disrupt fungal cell membrane integrity and inhibit spore germination. Clove is rich in eugenol, β-caryophyllene, and eugenyl acetate, exhibiting strong fungicidal activity against Candida species and other filamentous fungi. Turmeric contains curcumin, demethoxycurcumin, and ar-turmerone, which interfere with fungal growth and biofilm formation. Black pepper, which is rich in piperine, has demonstrated significant antifungal activity against Aspergillus niger.[27] Additionally, cardamom contains α-terpinyl acetate, 1,8-cineole, and limonene, which collectively disrupt fungal cell membranes and inhibit biofilm formation. Similarly, thymol and carvacrol, present in thyme and oregano, exert strong antifungal effects through membrane disruption and inhibition of fungal growth. Collectively, these phytochemicals act through multiple mechanisms to suppress fungal proliferation, thereby highlighting the potential of spice-derived compounds as natural antifungal agents.[28]

Although spices contain phytochemicals that frequently exhibit potent antifungal activity in vitro, their efficacy in vivo is often reduced or variable due to limitations in bioavailability, metabolism, tissue distribution limitations. Curcumin from turmeric, eugenol from clove, and cinnamaldehyde from cinnamon show robust in vitro inhibition but encounter poor water solubility, chemical instability, rapid metabolism, and low bioavailability in vivo.[29,30]

A limitation of this study is that antifungal activity was assessed only by the agar well diffusion method, and Minimum Inhibitory Concentration (MIC) and Minimum Fungicidal Concentration (MFC) values were not determined. While inhibition zones provide preliminary evidence of antifungal efficacy, future studies should include MIC and MFC analyses to better quantify the antifungal potential of spice extracts against Rhizopus oryzae.

Conclusion

In our present study, analysis of the influence of zinc and iron on the growth of Mucor organisms revealed that zinc does not facilitate the growth of R. oryzae and that iron supplements the growth of Mucor organisms. Thus, our study is in defiance with the hypothesis that zinc supports the growth of mucormycosis but in concurrence with the role of iron in enhancing the growth of fungal organisms. All four extracts of indigenous spices exhibited antifungal activity, with cinnamon exhibiting the maximum antifungal activity among all the extracts. Additionally, these findings open new avenues for investigating how spices hinder microbial growth. Future studies should determine the MIC and MFC values of these spice extracts and evaluate their efficacy in in vivo models to further establish their antifungal potential against Rhizopus oryzae.

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