GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Aspects of the virulence of medically important fungi

Ali A Alsudani * and Arjwan A Alsudani

Environmental Research and Pollution Prevention Unit, College of Science, University of Al-Qadisiyah, Iraq.

GSC Biological and Pharmaceutical Sciences, 2024, 28(02), 278–284

Publication history: Received on 15 July 2024; revised on 24 August 2024; accepted on 27 August 2024

Article DOI: https://doi.org/10.30574/gscbps.2024.28.2.0310

Abstract

Growing rates of immunodeficiency diseases, immunosuppression after transplantation, cancer, and cancer therapy are all contributing to the rise in fungal infections. They are widespread and may produce minor infections or more serious, deeply ingrained diseases that are fatal. Numerous virulence factors that support the survival and duration of the fungal infection cause tissue damage and illness within the host, these virulence factors are covered in this review. These elements include the capacity to cling to the tissues of hosts, the generation of tissue-damaging enzymes, and the direct disruption of host defense mechanisms. Mannitol and catalases are two substances produced by pathogenic fungi that offer protection against reactive oxygen species (ROS). Certain fungi such as Candida. albicans and dimorphic fungi are capable of changing their morphology. In a mammalian host, thermotolerance of at least 37°C is essential for life and aids in spread. Several pathogenic fungi synthesize melanin, which protects from extreme elements including UV rays, high temperatures, and ROS, another virulence determinant is the capacity of the host to access iron (Fe) in the storage or transport forms, and calcineurin functions as a pathogenic fungal sensor.

Keywords: Fungal infection; Pathogenic; Virulence; Dimorphism

1. Introduction

The frequency of fungal infections has increased, and this has led to a rise in both morbidity and death, the rise in immunodeficiency illnesses, including AIDS, cancer and its treatment, and immunosuppressive medication after transplantation, is particularly concerning for invasive fungal infections that pose a serious risk to life [1]. Because fungi are so common, infections can result via inhaling their spores (as in the case of *Aspergillus fumigatus*), from direct skin contact or implantation (as in the case of *Trichophyton rubrum*), or commensals (as in the case of *Candida albicans*) when the host's natural flora is altered, and the majority of immunocompetent people can, however, control and limit these fungal infections thanks to immunological systems [2, 3]. Fungi can cause a variety of diseases, including the common surface infections brought on by dermatophytes, invasive infections brought on by *C. neoformans* or *C. immitis*, additionally, *A. fumigatus* causes allergy diseases in atopic hosts, whereas invasive opportunistic infections happen in immunocompromised people, although mucocutaneous infections can occur in immunocompetent people [4, 5]. The fungal persistence and survival within the host are caused by specific virulence factors, causing tissue damage and illness, and the fungal capacity to induce disease [6]. These elements include the capacity to stick to the tissues of hosts, the synthesis of tissue-damaging enzymes, and the direct disruption of host defense mechanisms [7]. Certain fungus may change their shape; dimorphic fungi and *C. albicans* are two examples of this [8]. For a mammalian host to survive and aid in dispersal, thermotolerance, at least to 37°C, is essential [9]. So we try in this review article to understand these virulence characteristics is crucial as efforts to create medications and vaccines that are efficient in treating and preventing fungal infections continue.

* Corresponding author: Ali A Alsudani

2. Medically Important Pathogenic Fungi

Most fungi are classified as eukaryotes, that spread through the spore-producing process they are widely found in the environment and it is capable of both sexual and asexual reproduction, the majority of human pathogenic fungi are classified into three major phyla: Ascomycota, Basidiomycota, and Zygomycota [10].

2.1. Ascomycota

Due to their usage of ascospores for sexual reproduction, the fungus in this category are referred to as sac fungi (ascus), hyphae fuse to generate new cells during sexual reproduction, and these new cells divide to produce ascospores inside the ascus [11]. Additionally, they procreate asexually by the budding of their asexual spores, called conidia, and under favorable circumstances, asexual reproduction takes place in this phylum, dermatophytes, dimorphic fungi (*H. capsulatum*, *B. dermatitidis*, *P. brasiliensis*, *C. immitis* and *Candida* spp.), and septate filamentous fungus (*Aspergillus* spp.) are a few examples of harmful fungi [12].

2.2. Zygomycota

Rhizopus oryzae, *Mucor* spp., and *Rhizomucor* spp. are examples of fungi in this group that can cause invasive diseases, asexual reproduction occurs when zygomycetes produce sporangiospores, while sexual reproduction occurs when they create large, septate hyphae that spread quickly into colonies [13].

2.3. Basidiomycota

This group of fungi is recognized as "club fungi" as they generate spores that are sexual and have a structure resembling a club, these spores are called basidiospores, and they procreate asexually as well as sexually, they can be created in both terrestrial and aquatic habitats [14]. They are also capable of forming ballistospores, which are vehemently released into the air, such as *Trichosporon* spp., *Malassezia* spp., and *Cryptococcus* spp [15].

3. Pathogenetic Fungal Virulence Factors

Though there may be as many as 1.5 million fungal species on the planet, only approximately 600 are known to be harmful to humans, with about 30 of them being often linked to illness in humans [16]. The term "mycoses" refers to fungi that cause disease. Their virulence characteristics and capacity to cause illness stem from their ability to adapt to and endure in the hostile environment of their hosts [17]. Immunocompromised people are susceptible to infection by opportunistic pathogens, like *C. albicans*, *A. fumigatus*, and *C. neoformans*, primary pathogens are widely distributed and cause disease in immunocompetent hosts when inhaled in large doses, such as *H. capsulatum*, *C. immitis*, *B. dermatitidis*, and *P. brasiliensis* [18]. However, this distinction is not evident, as main pathogens like *C. immitis* can occasionally produce illness in immunocompetent people, while when a person's immune system is impaired, *C. neoformans* can cause serious illness [19].

3.1. Adhesins

Numerous virulence features, such as characteristics that enable them to adhere to tissues and withstand removal or carried away by ciliary activity or mucous, are what allow pathogenic fungi to cause illness [20]. For instance, *C. albicans* is known to possess a variety of adhesion molecules and may attach to medical equipment to build a biofilm, which increases the pathogenicity of the organism [21]. Hwp1p, Eap1p, Cshlp, Als proteins, and other molecules are examples of adhesion molecules, eight genes encode Als proteins, which are involved in cell-to-cell aggregation, and adhesion to collagen, laminin, endothelial cells, and epithelial cells [22]. The creation of vaccination to prevent invasive candidiasis is predicated on the abrogation of Als3, which mediates adhesion to platelets whereas Hwp1p facilitates binding to epithelium [23]. The hydrophobic protein rodlets that coat *A. fumigatus* conidia, and are encoded by the RODA and RODB genes facilitate the hyphae of *A. fumigatus* surface where the conidia are attached to albumin and collagen, the galactomannan, and chitin promote the binding of immunoglobulin and complement fibrinogen, and surfactants A and D [24, 25]. By binding to CR3 and CD14 on phagocytes and modifying host immune responses, BAD 1 helps *Blastomyces* sp. attach to host cells [26]. HSP60 is used by *H. capsulatum*, glyceraldehydes, and polypeptides are used by *P. brasiliensis*, and the spherule outer wall of *Coccidioides* sp. is used for attachment [27, 28].

3.2. Thermotolerance and Dimorphism

Morphogenesis is another way that pathogenic fungi acquire pathogenicity, the majority of pathogenic fungi display dimorphism, or the capacity to transform between a pathogenic and a non-pathogenic form since they are a part of their surroundings or as commensals, they take on a different morphotype when they infect others [29]. They can live as

molds or yeasts, the latter of which are ovoid or circular unicellular creatures through binary fission they generate a distinct, autonomous daughter cell during reproduction [30]. In contrast, molds are filamentous; they develop by extending apically to produce cellular units with septa dividing them but remain joined to the mold, these parts of the cell that branch out are referred to as mycelium or hyphae [31]. Certain fungi can have several morphotypes, for instance, *C. immitis* can produce big endosporulating spherules, and pseudohyphae are examples of intermediate forms that can exist, as demonstrated by *C. albicans* [32]. Additional virulence characteristic is the capability to grow in height temperatures, systemic infection-causing fungus may thrive at body temperature, as well as at 38-42°C, which is considered a febrile temperature because *A. fumigatus* is very thermophilic, it can tolerate temperatures between 55 to 77°C [33]. The majority of fungi live as a mold at room temperature, however pathogenic fungi convert into yeast at mammalian temperatures, and pathogenic fungi may also take on diverse forms at different temperatures [34]. Despite being virulent, *H. capsulatum* growth persisted at 37°C when the change from mycelia to yeast was inhibited [35]. Both forms of *C. albicans* are harmful, and they adapt to changes in their surroundings by becoming unicellular yeast at lower temperatures and an acidic pH that spreads throughout the environment, tissue invasion employs the hyphal form [36].

3.3. Capsules

Fungi that are capsules are often harmful, to fend against phagocytosis, *C. neoformans* covers itself in glucuronoxylomannan capsules, a capsular strain of *C. neoformans* is not virulent because it is easily phagocytosed; in contrast, environmental strains are weakly encapsulated, the capsules made of polysaccharides frequently predominant in isolates that cause infections [37]. Apart from the complement's depletion and the cytokine network's disruption, the encapsulation-causing genes include CAP 59 and CAP 64, furthermore preventing leucocytes from migrating to the infection site in the capsule [38, 39].

3.4. Enzyme production

Pathogenic fungi emit degradative enzymes that damage host tissue and impair the host's immune system, making it easier for disease to form and spread, extracellular phospholipases, lipases, and proteases are secreted by *C. albicans*, compared to commensal strains of *Candida* spp., pathogenic strains emit significantly more phospholipase, phospholipases A, B, C, and D break ester bonds and are essential for iron absorption and food consumption [40, 41]. Furthermore, aspartyl proteinases secreted by *C. albicans* hydrolyze complements, glycoproteins, immunoglobulin A, mucin, and lactoferrin, in addition to factor X, coagulation factors, and extracellular matrix proteins [42]. Lung tissue elastin is hydrolyzed by metalloprotease, phospholipases, and aspartic and serine proteases released by *A. fumigatus*, whereas serine proteases break down collagen, fibrin, and fibrinogen [43]. In addition, *C. neoformans* is known to attack the central nervous system by making urease, which is also used by *Coccidioides* spp., proteases, and phospholipases, such as lysophospholipase and lysophospholipase-transacylase, are also secreted by the fungus, the alkalinity of the infection sites is increased by these enzymes, which also degrade lung surfactant and promote adherence, variants that lack urease are unable to propagate [44].

3.5. Toxins

Aflatoxin and gliotoxin are just two of the toxins secreted by *A. fumigatus*, aflatoxin is hepatotoxic and carcinogenic, and it has no effect on the pathogenicity of *A. fumigatus*, due to its immune-suppressive properties, gliotoxin prevents T-cell activation and macrophage phagocytosis [45]. Additionally, it damages the epithelium and reduces ciliary action, which makes it much more difficult for the fungus cells to be removed [46]. Most other fungi produce a range of secondary metabolites, some of which are likely crucial in pathogenicity and have a wide range of cellular functions [47].

3.6. Melanin

Numerous pathogenic fungi produce melanin, which is hydrophobic and provides protection against extreme temperatures and UV radiation. It also protects reactive oxygen species [48]. Melanin has been demonstrated to avoid antifungal damage in *C. neoformans* and to impede antibody-mediated phagocytosis [49]. *A. fumigatus* similarly uses a six-gene route to generate melanin from acetate; other pathogenic fungus that also makes melanin includes *Blastomyces* spp., *P. brasiliensis*, and *H. capsulatum* [50, 51].

3.7. Protection from harmful nitrogen and oxygen molecules

By causing lipid peroxidation and nucleic acid breakage, neutrophils and macrophages inflict harm on fungus through oxidative processes, fungi that cause disease generate enzymes that shield them from the damaging effects of oxidation, to fend off ROS, and they generate catalases [52]. *C. neoformans* produces copper zinc, and peroxidase to withstand oxidation, but to protect itself against ROS, *C. albicans* uses HSP and superoxide dismutase [53, 54]. Along with

producing superoxide dismutase to shield it from oxidative damage, *A. fumigatus* also generates three catalases: Cat 1p, Cat 2p, and Cat-A associated with hyphae and conidia, respectively [55].

3.8. Acquisition of iron and the function of Mannitol and Calcineurin

The fungi require iron for development, respiration, and other metabolic functions; however, the host does not contain free iron, therefore, a virulence factor is the capacity to collect Fe from the host's storage or transit forms [56]. Three different modes of iron absorption are used by *A. fumigatus*: ferrous Fe uptake, mediated by siderophores Fe uptake, and reductase Fe uptake [57]. Iron is obtained by *C. albicans* by a variety of methods, including the usage of siderophores, and direct absorption from red blood cells' heme via hemoglobin surface-based receptors [58].

Particularly for CNS infections, mannitol is used by *C. neoformans*, where it shields the fungus from the damage caused by oxidation, and it may exacerbate cerebral oedema due to its high production [59]. Calcineurin detects the presence of harmful fungus there are various virulence factors whose expression is claimed to be influenced by it [60]. The growth of *A.* fumigatus depends on the calcineurin CNAA gene, which also facilitates tissue invasion [61].

4. Conclusion

It is essential to comprehend the processes of virulence due to the frequent and quick appearance of "new" fungal diseases as well as the re-emergence of "old" pathogens. As previously mentioned, fungi-related illnesses primarily impact individuals who are immunosuppressed or immunocompetent and are significant global sources of morbidity and mortality. Improvements in cancer treatments have led to a rise in the occurrences and related fatalities of invasive fungal infections. A variety of virulence factors that aid in fungal survival and persistence in the host, leading to tissue damage and disease, are responsible for some fungal species' capacity to cause disease. Understanding these virulence characteristics is crucial as efforts to create medications and vaccines that are efficient in treating and preventing fungal infections continue.

Compliance with ethical standards

Disclosure of conflict of interest

We declare no conflict of interest.

Authors' Contributions

Ali Alsudani wrote the first draft of the manuscript and reviewed and approved the final version, Arjwan Alsudani sourced for literature and reviewed the initial draft.

References

[1] Noël de Tilly, A., & Tharmalingam, S. (2022). Review of treatments for oropharyngeal fungal infections in HIV/AIDS patients. Microbiology Research, 13(2).

[2] Latgé, J. P., & Chamilos, G. (2019). Aspergillus fumigatus and Aspergillosis in 2019. Clinical microbiology reviews, 33(1), 10-1128.

[3] Kumar, S., Jain, T., & Banerjee, D. (2019). Fungal Diseases and Their Treatment: A Holistic Approach. Pathogenicity and Drug Resistance of Human Pathogens: Mechanisms and Novel Approaches, 111-134.

[4] Sykes, J. E. (2020). Fungal infections. Clinical Small Animal Internal Medicine, 985-1001.

[5] Gupta, C., Das, S., Gaurav, V., Singh, P. K., Rai, G., Datt, S. & Dar, S. A. (2023). Review on host-pathogen interaction in dermatophyte infections. Journal of Medical Mycology, 33(1), 101331.

[6] Leitão, J. H. (2020). Microbial virulence factors. International journal of molecular sciences, 21(15), 5320.

[7] Mba, I. E., & Nweze, E. I. (2020). Mechanism of Candida pathogenesis: revisiting the vital drivers. European Journal of Clinical Microbiology & Infectious Diseases, 39, 1797-1819.

[8] Min, K., Neiman, A. M., & Konopka, J. B. (2020). Fungal pathogens: shape-shifting invaders. Trends in microbiology, 28(11), 922-933.

[9] Almaguer Chávez, M. (2022). Thermotolerance and Adaptation to Climate Change. In The Impact of Climate Change on Fungal Diseases (pp. 37-71). Cham: Springer International Publishing.

[10] Liu, D. (2024). Classification of medically important fungi. In Molecular Medical Microbiology (pp. 2763-2777). Academic Press.

[11] Kosal, E. (2023). The Fungi Kingdom. Introductory Biology: Ecology, Evolution, and Biodiversity.

[12] Mankar, S. D., Vikhe, S., Pawar, T., & Bhawar, S. B. (2022). Current perspective of fungi-A review.

[13] Anjum, N. A. (2021). Mucormycosis: Botanical Insights Into The Major Causative Agents.

[14] Singara Charya, M. A. (2015). Fungi: an overview. Plant Biology and Biotechnology: Volume I: Plant Diversity, Organization, Function and Improvement, 197-215.

[15] Hernandez, H., & Martinez, L. R. (2018). Relationship of environmental disturbances and the infectious potential of fungi. Microbiology, 164(3), 233-241.

[16] Köhler, J. R., Hube, B., Puccia, R., Casadevall, A., & Perfect, J. R. (2017). Fungi that infect humans. Microbiology spectrum, 5(3), 5-3.

[17] Joao, I., Bujdáková, H., & Jordao, L. (2020). Opportunist coinfections by nontuberculous mycobacteria and fungi in immunocompromised patients. Antibiotics, 9(11), 771.

[18] Benninger, F., & Steiner, I. (2018). CSF in acute and chronic infectious diseases. Handbook of clinical neurology, 146, 187-206.

[19] Crum, N. F. (2022). Coccidioidomycosis: A contemporary review. Infectious Diseases and Therapy, 11(2), 713-742.

[20] Palmieri, F., Koutsokera, A., Bernasconi, E., Junier, P., von Garnier, C., & Ubags, N. (2022). Recent Advances in Fungal Infections: From Lung Ecology to Therapeutic Strategies With a Focus on Aspergillus spp. Frontiers in Medicine, 9, 832510.

[21] Angiolella, L. (2022). Virulence Regulation and Drug-Resistance Mechanism of Fungal Infection. Microorganisms, 10(2), 409.

[22] Lipke, P. N., Klotz, S. A., Dufrene, Y. F., Jackson, D. N., & Garcia-Sherman, M. C. (2018). Amyloid-like β-aggregates as force-sensitive switches in fungal biofilms and infections. Microbiology and Molecular Biology Reviews, 82(1), 10-1128.

[23] Valsecchi, I., Dupres, V., Stephen-Victor, E., Guijarro, J. I., Gibbons, J., Beau, R., & Beauvais, A. (2017). Role of hydrophobins in Aspergillus fumigatus. Journal of fungi, 4(1), 2.

[24] Valsecchi, I., Lai, J. I., Stephen-Victor, E., Pillé, A., Beaussart, A., Lo, V.,& Latgé, J. P. (2019). Assembly and disassembly of Aspergillus fumigatus conidial rodlets. The Cell Surface, 5, 100023.

[25] Heung, L. J. (2020). Monocytes and the host response to fungal pathogens. Frontiers in cellular and infection microbiology, 10, 34.

[26] Sullivan, D. C., & Nolan III, R. L. (2023). Blastomycosis. In Diagnosis and Treatment of Fungal Infections (pp. 267-278). Cham: Springer International Publishing.

[27] Campos, C. F., van de Veerdonk, F. L., Gonçalves, S. M., Cunha, C., Netea, M. G., & Carvalho, A. (2019). Host genetic signatures of susceptibility to fungal disease. Fungal Physiology and Immunopathogenesis, 237-263.

[28] Kumari, A., Tripathi, A. H., Gautam, P., Gahtori, R., Pande, A., Singh, Y., & Upadhyay, S. K. (2021). Adhesins in the virulence of opportunistic fungal pathogens of human. Mycology, 12(4), 296-324.

[29] Fernandes, K. E., & Carter, D. A. (2020). Cellular plasticity of pathogenic fungi during infection. PLoS Pathogens, 16(6), e1008571.

[30] Money, N. P. (2016). Fungal cell biology and development. In The fungi (pp. 37-66). Academic Press.

[31] Shange, P. M. (2020). Reverse Fountain Cytoplasmic Streaming in Rhizopus oryzae (Master's thesis, Arizona State University).

[32] Jiranek, J., Miller, I. F., An, R., Bruns, E., & Metcalf, C. J. E. (2023). Mechanistic models to meet the challenge of climate change in plant–pathogen systems. Philosophical Transactions of the Royal Society B, 378(1873), 20220017.

[33] Sun, S., Hoy, M. J., & Heitman, J. (2020). Fungal pathogens. Current Biology, 30(19), R1163-R1169.

[34] Mittal, J., Ponce, M. G., Gendlina, I., & Nosanchuk, J. D. (2019). Histoplasma capsulatum: mechanisms for pathogenesis. Fungal Physiology and Immunopathogenesis, 157-191.

[35] Zdanavičienė, E., Sakalauskienė, J., Gleiznys, A., Gleiznys, D., & Žilinskas, J. (2017). Host responses to Candida albicans. A review. Stomatologija, 19(4), 109-23.

[36] Ciurea, C. N., Kosovski, I. B., Mare, A. D., Toma, F., Pintea-Simon, I. A., & Man, A. (2020). Candida and candidiasis—opportunism versus pathogenicity: a review of the virulence traits. Microorganisms, 8(6), 857.

[37] Wear, M. P., Jacobs, E., Wang, S., McConnell, S. A., Bowen, A., Strother, C., ... & Casadevall, A. (2022). Cryptococcus neoformans capsule regrowth experiments reveal dynamics of enlargement and architecture. Journal of Biological Chemistry, 298(4).

[38] Tashak Golroudbari, H., Banikarimi, S. P., Ayati, A., Hadizadeh, A., Khorasani Zavareh, Z., Hajikhani, K., & Ahmadi Tafti, H. (2023). Advanced micro-/nanotechnologies for exosome encapsulation and targeting in regenerative medicine. Clinical and Experimental Medicine, 1-22.

[39] Ma, H., Xing, F., Zhou, Y., Yu, P., Luo, R., Xu, J., & Ritz, U. (2023). Design and fabrication of intracellular therapeutic cargo delivery systems based on nanomaterials: current status and future perspectives. Journal of Materials Chemistry B.

[40] Laird, M. R. (2020). Determination of the Role of Glucose and pH in the Production of Biofilms, Phospholipase and Protease in Candida auris (Doctoral dissertation, University of Central Lancashire).

[41] Ruiz-Moyano, S., Pérez-Nevado, F., Rodríguez, A., Córdoba, M. G., Martín, A., & Córdoba, J. J. (2024). Pathogenesis of fungal infections. In Molecular Medical Microbiology (pp. 2797-2812). Academic Press.

[42] Bras, G., Satala, D., Juszczak, M., Kulig, K., Wronowska, E., Bednarek, A., ... & Karkowska-Kuleta, J. (2024). Secreted aspartic proteinases: key factors in Candida infections and host-pathogen interactions. International Journal of Molecular Sciences, 25(9), 4775.

[43] Biswas, P., Mukherjee, G., Singh, J., Rastogi, A., & Banerjee, R. (2021). Enzymes in health care: Cost-effective production and applications of therapeutic enzymes in health care sector. Bioprospecting of enzymes in industry, Healthcare and Sustainable Environment, 291-314.

[44] Kumari, A., Tripathi, A. H., Upadhyay, S. K., Gupta, T. M., & Prakash, P. Y. (2024). Enzymes conferring virulence traits among human pathogenic fungi. In Enzyme Biotechnology for Environmental Sustainability (pp. 339-362). Academic Press.

[45] Egbuta, M. A. (2015). An approach to understanding toxicity induction by filamentous fungi on human cell lines (Doctoral dissertation, North-West University (South Africa), Mafikeng Campus).

[46] Roe, K. (2024). The epithelial cell types and their multi-phased defenses against fungi and other pathogens. Clinica Chimica Acta, 119889.

[47] Khan, R. A. A., Najeeb, S., Hussain, S., Xie, B., & Li, Y. (2020). Bioactive secondary metabolites from Trichoderma spp. against phytopathogenic fungi. Microorganisms, 8(6), 817.

[48] Eisenman, H. C., Greer, E. M., & McGrail, C. W. (2020). The role of melanins in melanotic fungi for pathogenesis and environmental survival. Applied microbiology and biotechnology, 104, 4247-4257.

[49] Oliveira, L., Ferrarini, M., Dos Santos, A. P., Varela, M. T., Corrêa, I. T. S., Tempone, A. G., & Pascon, R. C. (2020). Coumaric acid analogues inhibit growth and melanin biosynthesis in Cryptococcus neoformans and potentialize amphotericin B antifungal activity. European Journal of Pharmaceutical Sciences, 153, 105473.

[50] Lim, W., Verbon, A., & van de Sande, W. (2022). Identifying novel drugs with new modes of action for neglected tropical fungal skin diseases (fungal skinNTDs) using an Open Source Drug discovery approach. Expert Opinion on Drug Discovery, 17(6), 641-659.

[51] Salgado-Castillo, S. N., López-Peña, H. A., Díaz, R., Peña-Solis, K., Ponce-Alquicira, E., Soriano-Santos, J., & Díaz-Godínez, G. (2023). Fungal melanins and their potential applications: A Review. BioResources, 18(4), 8688.

[52] Dutta, S., Sengupta, P., Slama, P., & Roychoudhury, S. (2021). Oxidative stress, testicular inflammatory pathways, and male reproduction. International journal of molecular sciences, 22(18), 10043.

[53] Hernández-Chávez, M. J., Pérez-García, L. A., Niño-Vega, G. A., & Mora-Montes, H. M. (2017). Fungal strategies to evade the host immune recognition. Journal of Fungi, 3(4), 51.

[54] Shishodia, S. K., & Shankar, J. (2020). Proteomic analysis revealed ROS-mediated growth inhibition of Aspergillus terreus by shikonin. Journal of proteomics, 224, 103849.

[55] Rouein, S., Ghasemi, F., & Badiee, P. (2020). Compare catalase activity between Aspergillus flavus and A. fumigatus, isolated from clinical and environmental specimens. Jundishapur Journal of Microbiology, 13(8).

[56] Murdoch, C. C., & Skaar, E. P. (2022). Nutritional immunity: the battle for nutrient metals at the host–pathogen interface. Nature Reviews Microbiology, 20(11), 657-670.

[57] Moloney, N. M., Owens, R. A., Meleady, P., Henry, M., Dolan, S. K., Mulvihill, E., & Doyle, S. (2016). The iron-responsive microsomal proteome of Aspergillus fumigatus. Journal of Proteomics, 136, 99-111.

[58] Duval, C., Macabiou, C., Garcia, C., Lesuisse, E., Camadro, J. M., & Auchère, F. (2020). The adaptive response to iron involves changes in energetic strategies in the pathogen Candida albicans. Microbiologyopen, 9(2), e970.

[59] Watkins, R. A., King, J. S., & Johnston, S. A. (2017). Nutritional requirements and their importance for virulence of pathogenic Cryptococcus species. Microorganisms, 5(4), 65.

[60] de Andrade, I. B., Corrêa-Junior, D., Alves, V., Figueiredo-Carvalho, M. H. G., Santos, M. V., Almeida, M. A., ... & Frases, S. (2023). Cyclosporine affects the main virulence factors of Cryptococcus neoformans in vitro. Journal of Fungi, 9(4), 487.

[61] Liu, C., Liu, T., Lv, Z., Qin, M., Qu, Z., Zhang, Z., ... & Shen, M. (2022). A calcineurin regulator MoRCN1 is important for asexual development, stress response, and plant infection of Magnaporthe oryzae. Frontiers in Plant Science, 13, 925645.