

## Melanin Pigment production by Fungal Cells and Functions of Fungal Melanin in the various applications

Wijdan Ahmed Ali // University Of Anbar , College of Science , Department of Biology

### Abstract:

The study provides a broad overview of all forms of melanin found in various species. Melanin is usually handled independently from comparable fungal or bacterial pigments since it is thought to be an animal cutaneous pigment. Melanin's are aged biological pigments present in all domains of life. Their function in microbial pathogenicity is well recognized in fungi; nevertheless, these complex macromolecules let fungal pathogens survive in extreme environments including the Earth's poles, the International Space Station, and areas polluted by radioactive substances and ionizing radiation. Melanin is a pigment that retains and accumulates carbon because of its capacity to connect with a wide variety of wavelengths of electromagnetic radiation. Free radical scavenging, thermotolerance, Melanin can also benefit an ectotherm who lives in frigid areas with limited quantities of sun exposure, according to new research. Melanin's thermoelectric influence in air creates a positive thermoelectric voltage. Melanin can also aid an ectotherm living in cold regions with limited solar exposure, which can be troublesome in dry tropical climates due to the risk of overheating. In this paper, we will look at the specific roles of melanin pigment. Fungal pigments have been found to have anti-cancer and anti-tumor properties. In addition, cosmetic companies are seeking for new natural pigments to replace synthetic forms. In this research, we'll look into the specific roles. Fungal melanin is involved in metal ion sequestration, cell growth, and cellular mechanical-chemical energy.

**Keyword:** thermal melanism, black fungus, Biological Roles, industrial Applications.

### إنتاج صبغة الميلانين بواسطة الخلايا الفطرية

### ووظائف الميلانين الفطرية في التطبيقات المختلفة

وجدان احمد علي // جامعة الانبار - كلية العلوم - قسم علوم الحياة

### الخلاصة:

قدمت الدراسة نظرة عامة واسعة على جميع أشكال الميلانين الموجودة في الأنواع المختلفة. عادة ما يتم التعامل مع الميلانين بشكل مستقل عن الأصباغ الفطرية أو البكتيرية المماثلة حيث يُعتقد أنه صبغة جلدية حيوانية. صبغات الميلانين هي أصباغ بيولوجية قديمة موجودة في جميع مجالات الحياة. وظيفتها في الأمراض الميكروبية معترف بها جيدًا في الفطريات؛ ومع ذلك، فإن هذه الجزيئات المعقدة تسمح لمسببات الأمراض الفطرية بالبقاء على قيد الحياة في البيئات القاسية بما في ذلك قطبي الأرض، ومحطة الفضاء الدولية، والمناطق الملوثة بالمواد المشعة والإشعاع المؤين. الميلانين هو صبغة تحافظ على الكربون وتراكمه بسبب قدرته على الاتصال بمجموعة متنوعة من الأطوال الموجية للإشعاع الكهرومغناطيسي. إزالة الجذور الحرة، والتحمل الحراري.

ممكن أن يستفيد الميلانين أيضًا من الحرارة الخارجية التي تعيش في مناطق متجمدة بكميات محدودة من التعرض لأشعة الشمس، وفقًا للأبحاث الجديدة. يخلق التأثير الكهروحراري للميلانين في الهواء جهدًا كهربائيًا حراريًا إيجابيًا. وهذا يمكن أن يساعد الميلانين للذين يعيشون في المناطق الباردة مع التعرض المحدود للشمس، والذي يمكن أن يكون مزعجًا في المناخات الاستوائية الجافة بسبب خطر ارتفاع درجة الحرارة. في هذا البحث، سننظر في الأدوار المحددة لصبغة الميلانين فقد تم العثور على الأصباغ الفطرية التي لها دور وخصائص مضادة للسرطان ومضادة للأورام، إضافة إلى أن شركات مستحضرات التجميل تسعى للحصول على أصباغ طبيعية جديدة لتحل محل الأشكال الاصطناعية.. يشارك الميلانين الفطري في عزل أيونات المعادن، ونمو الخلايا، والطاقة الميكانيكية والكيميائية الخلوية.

الكلمات المفتاحية: الميلانين الحراري، الفطريات السوداء، الأدوار البيولوجية، التطبيقات الصناعية .

## Introduction

Fungal melanin's perform several biological roles including photo protection, energy recycling by easily processing and transducing electromagnetic radiation, as well as thermoregulation Free radical and metal binding are other functions of fungal melanin, as well as dehydration defense, chemical and mechanical stresses as well as the condition of fungal growth. Humic substances (HS), which are dark-colored organic compounds generated via chemical and biological transformation of mostly plant leftovers but also animal and human wastes, are another significant carbon deposit in nature. Phenols, quinones, carbohydrates, as well as larger molecular mass components including lignins, polysaccharides, and melanins, are the primary building blocks of HS. based substances such as chlorophylls, bilirubin, hemoglobin, hemocyanin as melanins, tannins and cutins Microorganisms, particularly fungi that produce oxidizing enzymes, are crucial in the production, breakdown, transformation, and mineralization of HS. (1), (2). Melanin has a structure that is both varied and heterogeneous. This is owing to the fact that melanin comes from a variety of places, resulting in variability in composition, size, color, and function. Furthermore, melanin's physical characteristics (strong negative charge, large molecular weight, and hydro-

phobic nature) make it difficult to detect and define its structure using analytical methods (3). Melanins are a type of biological pigment that is unlike any other. Due to their variety and structural complexity, Eumelanins, pheomelanins, neuromelanins, and allomellalins are the four types of melanins (4). Melanin and polyphenolic pigments are multifunctional polymers with a wide range of aesthetic and defensive functions in the living world adhesive, photonic, electrical, and radiation-protective materials and coatings continue to be inspired by these polymeric pigments. , such as optical broadband absorption and paramagnetism movement of charges Melanins may perform a variety of tasks in biological processes related to these characteristics, and melanisation is a generic response to climatic change (5),(6). The pervasive existence of melanins in the genetics suggests a fundamental significance in the development of life on Earth for this type of biomolecules. Melanotic, black, dematiac, microcolonial, or meristematic fungus are examples of constitutively melanized fungi. Many fungal organisms which could be named "facultative melanotic" fungi under certain circumstances just melanised. Phylogenetically complex melanotic fungi occur. Melanin is produced by fungi through a variety of biosynthetic routes. However, it is widely assumed that ascomycetes fungus generates melanin from 1,8 di-

hydroxynaphthalene (DHN), whereas basidiomycetes fungi create catechol melanin from -glutaminy-3,4-dihydroxybenzene precursor, commonly known as GDHB melanin, and less frequently from L-dihydroxyphenylalanine (L-Dopa) (3). During the production of melanin, the phenolic precursors go through numerous reduction and oxidation stages, which can happen enzymatically by polymerizations. In addition, also in the absence of enzymes, a transparent solution of L-Dopa aqueous can sediment into melanin particles at room temperature (7). Melanin synthesis is dependent on the enzyme diphenol oxidase, which is encoded by two genes, LAC1 and LAC2, with Lac1 being the most important protein involved in the pigment's formation (8). Human melanin and fungal melanin may have similar functional groups and physicochemical properties. Due to the vast variety of melanotic organisms and metabolic processes involved in the synthesis of melanin, fungal melanins are likely to appear, it is frequently unknown. (9). Melanin is present on the cell surface of fungus and is also discharged into the extracellular environment. Melanin granules can be located between the plasma membrane and the cell wall's innermost layer for example in *Cryptococcus neoformans*. When chitin production is disrupted, it is released into the environment, resulting in a phenotype known as "leaky melanin." In *C. neo-*

*formans* melanin isolates, traces of NMR chitin signals are common (10).

This indicates that these polysaccharides are strongly connected with the pigment in order to survive hydrolysis during melanin preparations. Melanin has a significant impact on *C. neoformans* biology and pathogenicity, the pathogenicity of mutants who are unable to melanize is significantly reduced this pigment is widely recognized for conferring resistance to a variety of stress conditions, including free radicals, ionizing radiation, and heat. It can also bind to antifungal medicines, making them less effective. Intriguingly, a recent research found that cryptococcal melanin improves heat uptake and so helps to low-temperature growth. (11).

According to a new research, In *Aspergillus*, melanin manufacturing begins in internal endosomes, which are released into the cell wall in a unique manner, allowing additional melanin producing enzymes to accumulate (12).

### **Melanin's Functions with Fungi**

A single melanin-producing melanocyte is surrounded by epidermal cells and other cell types in the melano-epidermal unit. Melanosomes create a crucial barrier/shield of DNA in the cytoplasm of keratinocytes, exhibiting photoprotection, by producing perinuclear caps. Melanin production, distribution, type, and quantity all influence the skin's physiological

reaction to UV light (13).

Melanins have physicochemical and structural properties that no other pigment can match (14). Our capacity to grasp melanin's synthesis and, as a result, its functions is limited by its basic dynamic character. Physicochemical investigations have provided helpful insights into the characteristics that underpin their diverse biological roles in eukaryotic activities in recent years. (15). Another effective defensive mechanism of melanins is their ability to absorb a wide range of electromagnetic radiation, shielding fungus from damaging radiation such as UV light (16),(17). In fungus, increased melanin synthesis is linked to increased resistance to gamma radiation. Melanized fungus are more resistant to space radiation (18), and they can thrive in highly high ionizing radiation environments, such as the Chernobyl contaminated reactor (19). *C. neoformans* and *Exophiala* (Wangiella) dermatitidis are protected by melanin against extremes in temperature, both hot and cold. It also protects fungus from heavy metals that are prevalent in the environment. (20), (21). Melanized *C. neoformans*, for example, are less sensitive to silver nitrate than non-melanized cells. Melanin chelates silver nitrate, a substance that would otherwise be extremely toxic to fungi and bacteria, providing this protection by boosting the expression of melanin production genes in response to the

silver nanoparticles. As a result, fungal melanins have a wide spectrum of protective functions against a variety of environmental stresses (22), (23).

In a number of fungal species, melanin is a major virulence component that acts as a non-specific shield during infection (24). All evident biological roles of fungal melanization outside of the human host. We shall examine the specific roles of fungal melanins on the following pages, in light of certain generic physicochemical characteristics found for non-fungal melanins (25).

### Photoprotection

Melanin is thought to have a function in photoprotection by serving as a natural sunscreen on the epidermis. Although many biological pigments may only consume a narrow range of light frequencies, melanins can absorb a broad band of electromagnetic radiation, shielding fungus from damaging UV rays. (17),(18). Synthetic and natural melanin optical absorption curves, exhibiting peaks in the UV zone and decreases as it approaches near infrared frequencies. Despite the fact that all melanins should have the same color, the optical characteristics of specific fungal melanins are largely unknown, and they may differ substantially between species while having the same wide spectrum light absorption (26). Ionizing radiation causes fungal melanogenesis, which is similar to human skin tanning. It's

crucial to note that black fungus can withstand levels of ionizing radiation that would kill any other eukaryote. Changes in the chemical content and structure of melanin are all possible ways for fungal melanin to protect a cell from radiation (27). The amount of radiation, the kind of irradiation, and the type of melanin all influence the potential for photoprotection after a certain amount of irradiation, photoprotection can change into photo-damage, since melanin can form cytotoxic radical organisms. As a result, the existence of melanin may result in a higher sensitivity to radiation respond to Melanoma on the Skin in specific conditions. (28).

It is self-evident that exposure to sunlight offers a range of health benefits. Visible radiation is required for the sensation of sight in mammals and the control of circadian rhythms, in addition to its function in photosynthesis in plants and microbial algae. UV radiation has a number of beneficial properties for human skin, including antimicrobial properties and the ability to promote wound healing. UV-induced ring B opening promotes antibacterial activity, wound healing, and jaundice avoidance, as well as the production of active vitamin D from sterol precursors (29).

Photoprotectors, on the other hand, are made from natural compounds or alcoholic extracts derived from natural sources like marine and plants creatures. In reality, this ap-

proach has been used in a variety of ways throughout history, and many of them are taken from historical recipes for various purposes, but some of them might be perfect sunscreen filtrates (30).

### Antioxidant

Melanins are powerful antioxidants that aid fungal virulence by engaging with host defense mechanisms such as the suppression of phagocytic cell oxidative bursts (31). Fungal melanins may also provide protection against hypochlorite, permanganate, and hydrogen peroxide. Melanins are stable free radical molecules that may respond to magnetic fields, explaining their paramagnetic properties for oxidized or minimized metals. Melanins were used as sites for the synthesis of metal nanoparticles by fungal melanins. (32). Melanin pigments retain their capacity to absorb heavy metals and harmful electrophilic metabolites, as well as deactivate free radicals and peroxides. Iron ion sequestration has been recognized as a significant mechanism for melanin's inhibitory effects on lipid peroxidation. As a result, these pigments have a lot of antioxidant activity (33),(34).

Antioxidants, however, are generally tyrosinase inhibito. The inhibition of melanogenesis is a frequent therapy for hypopigmentation. In the literature on skin pigmentation, there are several reviews on the construction and effects of tyrosinase inhibi-



tors. These compounds, which are primarily found in plants and herbs, inhibit melanogenesis by decreasing the expression of certain genes. (35),(36).

### Energy harvesting

Chlorophyll has long been thought to be the most important light-absorbing pigment in photosynthesis. Without this pigment, no creature is known to be able to perform photosynthesis. However, there is a new, previously unknown player in the field: melanin. Melanin has the previously unknown ability to absorb visible and invisible light and convert it to chemical energy via the dissociation of water molecules. (37). This function was predicated on the presence of melanotic microorganisms in certain environments, as well as the attraction of fungal growth to sources of radiation ( phenomenon known as radiotropism) ( 38).

Experimental proof was obtained by (39) that fungal melanin mediates a process for converting light energy into useable metabolic energy. The degree of cell melanisation and the amount of radiation exposure determine how quickly melanotic fungus grow because of Melanins may absorb a wide variety of radiation wavelengths, including gamma rays, X-rays, and ultraviolet (UV) light. As a result, they may now be found in a wide range of fungi as effective photoprotectants. Some melanotic

fungus, such as *Cryptococcus neoformans*, *Alternaria* and *Aspergillus* have enhanced radiation tolerance by growing toward sources of radiation (40). The hydration condition of melanins has a substantial impact on their ability to transmit electric energy, showing that water is an essential component of the load transmission process (37),(39). In contrast to the conventional amorphous semiconductor concept, recent investigations have revealed that in air, the thermoelectric impact of melanin produces a positive thermoelectric voltage, which is unusual for resistive behavior. Experts now characterize melanin as a porous mixed conductor in which the main charge shifts from electrons to protons as hydration rates rise. Melanin's electroconductive characteristics make it a good candidate of environmentally friendly electronics. (41).

### Thermoregulation

Melanin's ability to absorb sun energy efficiently and disperse it non-radiatively as heat is one of its functions in thermoregulation. Melanin, like a dark body, consumes the lightest and reflects just a little portion of the light absorbed. The impact of this energy absorption is determined by several factors, including melanin type, luminous strength, and moisture level. Free radicals may build as a result of part of the energy absorbed (34).

Ectotherms rely on the increase and fall of body temperature in relation to the temperature of the surrounding environment. Although ectotherms, like other living organisms, produce some metabolic heat, they are unable to enhance this heat production in order to maintain a certain internal temperature. As a result, melanin-mediated heat intake from sunlight is critical. It differs from endothermic ('warm-blooded') animals, which rely on food metabolism to keep their body temperatures stable, the capacity of melanotic animals to absorb and convert electric radiation. Melanin can also help an ectotherm who lives in cold climates with low amounts of solar exposure, which can be problematic in dry tropical climates owing to the risk of overheating. The ectothermic thermal melanism theory, which may forecast its geographical distribution and ecology, is based on such principles (42). *Wangiella* [Exophiala] dermatitidis has been documented protecting against heat stress, *Conidia* generated by *Monilia fructicola* mutants lacking melanin were high sensitive to this conditions. As defensins, magainins, and protegrins are kinds of fungicidal and bactericidal proteins present in mammals, this pigment inhibits the conidia from being digested by competing microbes' proteases and hydrolases (43),(44).

### Resistance of Melanin pigment

Melanin pigment is so robust and durable that it is able to survive the fossilization cycle, whereas other organic macromolecules decay and vanish. These structural consistencies over long periods of time often illustrates melanin's marked role as a transducer of energy and indicates intriguing thermodynamic properties. (45). Manganese and lignin peroxidases have been found in a range of fungus species with strong melanolytic activity *Aspergillus fumigatus* may breakdown melanin (46).

### protection and adaptation

The ectomycorrhizal *Cenococcum geophilum* suppresses melanin synthesis, leading in reduced osmotic stress and drying susceptibility (47) Fungal melanin can guard against desiccation by improving cells' capacity to consume and hold water (48). An ideal pigment-producing microbe should be able to use a variety of C and N sources, pH, temperature, and mineral concentration tolerant, and produce a fair amount of pigments. Nontoxic and nonpathogenic properties, as well as ease of separation from cell biomass, are other desirable characteristics. It is critical to discover the nutritional and physical variables that have a stronger impact on cell development and metabolite production in order to enhance performance and lower the cost of colors generated by microbial fermentation (49).

### **Anticancer Potential of Fungal Pigments**

Anticancer and antitumor activities have been discovered in fungal pigments. In numerous studies, fungal pigments have been discovered as a potential anticancer treatment. Cell cycle inhibition and death are known to be properties of this microbial pigment. Fungi, among microorganisms, have the capacity to generate chemicals with antibacterial, anticancer, anti-mutagenic, and anti-viral properties, biosynthesises a variety of alkaloids, terpenoids, steroids, phenolics, quinones, and pheromones. These metabolites have been linked to phytoxic, cytotoxic, antifungal, antibacterial, and anticancer properties (50). Mouse skin carcinoma, human laryngeal carcinoma, human colon adenocarcinoma, human hepatocellular carcinoma, and other fungal pigments have been found to have anticancer/antitumor potential against a range of malignancies (51) include norsolorinic acid from *A. nidulans*, shiraiarin from *Shiraia bambusicola*, alterporriol K, alterporriol L, and alterporriol M from *Alternaria spp.*, benzoquinone from *Fusarium spp.*, With a red pigment from *Fusarium chlamydosporum* that has yet to be named (52)

Malignant melanoma, sometimes known as “the cancer that rises with the Sun,” is one of the most aggressive human tumors and has the poorest prognosis of all skin malignancies

due to the failure of traditional therapies like radiation and chemotherapy. Melanomas account for just 4% of all dermatologic malignancies, yet they are responsible for more than 80% of all skin cancer-related fatalities between 1975 and 2013, A variety of host characteristics and sun exposure circumstances have been identified as skin melanoma risk factors (53).

### **Fungal Pigments in the Cosmetic Industry**

As the demand for natural goods grows, cosmetic manufacturers are looking for new forms of natural pigments to replace synthetic colors. The usage of fungal pigments in cosmetics is fast increasing due to their benefits. Cosmetics, sunscreens, sun lotions, sunblock face creams, anti-aging facials, and other products containing fungal pigments such as melanin, carotenoids, and lycopene have all been shown to include fungal pigments (54) Fungi include a variety of physiologically significant active chemicals The fruiting bodies of several species of basidiomycetes are utilized in traditional treatments and cosmetics. Mushrooms include a variety of chemicals that are utilized in nutraceuticals. The results of such compounds come in a variety of shapes and sizes such a creams, lotions, applied topically and ointments (55), (56).



## Conclusion

Melanin's physicochemical characteristics and biological activity make it an ideal biomaterial for a variety of cosmetic, medicinal, electrical, and food processing applications. Furthermore, this pigment is biotechnologically interesting since it can be produced in large numbers at a low cost, making its use in practical applications in the future economically possible. However, more information on structure-property-function relationships is needed in order to develop melanin-based technology. Furthermore, the substance will be helpful and will encourage additional research into fungal melanin, which might aid in the development of innovative and sustainable solutions for human health and the environment.

## Reference

- (1) Grzegorz Janusz, Anna Pawlik, Urszula Swiderska-Burek, Jolanta Polak, Justyna Sulej, Anna Jarosz-Wilkolazka and Andrzej Paszczyński. 2020. Laccase Properties, Physiological Functions, and Evolution Int. J. Mol. Sci. 21, 966; doi:10.3390/ijms21030966.
- (2) Lan Lin and Jianping Xu. 2020. Fungal Pigments and Their Roles Associated with Human Health. J. Fungi, 6, 280.
- (3) Anh N. Tran Ly, Carolina Re, Francis W. M. R. Schwar and Javier Ribera. 2020. Microbial production of melanin and its various applications. World Journal of Microbiology and Biotechnology. 36:170.
- (4) Ambrico M, 2016 SPECIAL ISSUE: Melanin, a long lasting history bridging natural pigments and organic bioelectronics. Polymer International 65, 1249-1250.
- (5) Ayala Lampel, Scott A. McPhee, Salma Kassem, Deborah Sementa, Tlalit Massarano, James M. Aramini, Ye He, and Rein V. Ulijn. 2021. Melanin-Inspired Chromophoric Microparticles Composed of Polymeric Peptide Pigments. J. of the German chemical society, v.60; Issue 14. p.7564-7569.
- (6) Roulin A, 2014 Melanin-based colour polymorphism responding to climate change. Glob Chang Biol 20, 3344-3350. [PubMed: 24700793].
- (7) Helene C. Eisenman. 2012. Synthesis and assembly of fungal melanin. Appl Microbiol Biotechnol. February; 93(3): 931-940. doi:10.1007/s00253-

- 011-3777-2.
- (8) Oscar Zarag.2019. Basic principles of the virulence of *Cryptococcus oza*. VIRULENCE, VOL. 10, NO. 1, 490-501
- (9) Solano F, 2016 Photoprotection versus photodamage: updating an old but still unsolved controversy about melanin. *Polymer International* 65, 1276-1287.
- (10) Dong C, Yao Y, 2012 Isolation, characterization of melanin derived from *Ophiocordyceps sinensis*, an entomogenous fungus endemic to the Tibetan Plateau. *Journal of Bioscience and Bioengineering* 113, 474-479. [PubMed: 22261188].
- (11) Cordero RJB, Robert V, Cardinali G.2018.Impact of yeast pigmentation on heat capture and latitudinal distribution. *Curr Biol.* 2018; 28:2657-64 e3.
- (12) Radames JB Cordero, Arturo Casadevall.2019. Functions of fungal melanin beyond virulence. *Fungal Biol Rev.* March; 31(2): 99-112. doi: 10.1016/j.fbr.2016.12.003.
- (13) Huang, Y.; Li, Y.; Hu, Z.; Yue, X.; Proetto, M.T.; Jones, Y.; Gianneschi, N.C. 2017. Mimicking melanosomes: Polydopamine nanoparticles as artificial microparasols. *ACS Cent. Sci*, 3, 564-569.
- (14) Perez-Cuesta, U.; Aparicio-Fernandez, L.; Guruceaga, X.; Martin-Souto, L.; Abad-Diaz-de-Cerio, A.; Antoran, A.; Buldain, I.; Hernando, F.L.; Ramirez-Garcia, A.; Rementeria, A.2020. Melanin and pyomelanin in *Aspergillus fumigatus*: From its genetics to host interaction. *Int. Microbiol*, 23, 55-63.
- (15) Abbas M, D'Amico F, Morresi L, Pinto N, Ficcadenti M, Natali R, Ottaviano L, Passacantando M, Cuccioloni M, Angeletti M, Gunnella R, 2009 Structural, electrical, electronic and optical properties of melanin films. *Eur Phys J E Soft Matter* 28, 285-291. [PubMed: 19190947] .
- (16) Geib, E., Gressler, M., Viediernikova, I. 2016. A non-canonical melanin biosynthesis pathway protects *Aspergillus terreus* conidia from environmental stress. *Cell Chemical Biology* 23, 587-597. doi: 10.1016/j.chembiol.2016.03.014.
- (17) Bennet, D., Kim, S., 2015. Evaluation of UV radiation-induced toxicity and biophysical changes in various skin cells with photo-shielding molecules. *The Analyst* 140, 6343-6353. doi:10.1039/c5an00979k.
- (18) Gomoiu, I., Chatzitheodoridis, E., Vadrucchi, S., Walther, I., Cojoc, R., 2016. Fungal spore's viability on the international space station. *Origins of Life and Evolution of Biospheres* 1-16. doi:10.1007/s11084-016-9502-5.
- (19) Radames JB Cordero, Arturo Casadevall.2019. Functions of fungal melanin beyond virulence. *Fungal Biol Rev.* March; 31(2): 99-112. doi: 10.1016/j.fbr.2016.12.003.
- (20) Perfect JR, Wong B, Chang YC, Kwon-Chung KJ, Williamson PR, 1998 *Cryptococcus neoformans*: virulence and host defences. *Med Mycol* 36 Suppl 1, 79-86. [PubMed: 9988495] .
- (21) Fogarty, R.V.; Tobin, J.M. Fungal melanins and their interactions with met-

- als. *Enzym. Microb. Technol.* 1996, 19, 311-317. [CrossRef]
20. Smith, D.F.Q.; Casadevall, A. The role of melanin in fungal pathogenesis for animal hosts. *Curr. Top. Microbiol. Immunol.* 2019, 422, 1-30.
- (22) Mishra S, Singh HB .2015. Silver nanoparticles mediated altered gene expression of melanin biosynthesis genes in *Bipolaris sorokiniana*. *Microbiol Res* 172:16- 18. <https://doi.org/10.1016/j.micres.2015.01.006>.
- (23) Tsirilakis K, Kim C, Vicencio AG, Andrade C, Casadevall A, Goldman DL, 2012 Methylxanthine inhibit fungal chitinases and exhibit antifungal activity. *Mycopathologia* 173, 83-91. [PubMed: 21968902] .
- (24) Perfect JR, Wong B, Chang YC, Kwon-Chung KJ, Williamson PR, 1998 *Cryptococcus neoformans*: virulence and host defences. *Med Mycol* 36 Suppl 1, 79-86. [PubMed: 9988495] .
- (25) Pacelli, C.; Cassaro, A.; Maturilli, A.; Timperio, A.M.; Gevi, F.; Cavalazzi, B.; Stefan, M.; Ghica, D.; Onofri, S.2020. Multidisciplinary characterization of melanin pigments from the black fungus *Cryomyces antarcticus*. *Appl. Microbiol. Biotechnol*, 104, 6385-6395.
- (26) Meredith P, Sarna T, 2006 The physical and chemical properties of eumelanin. *Pigment Cell Res* 19, 572-594. [PubMed: 17083485].
- (27) Selbmann L, Isola D, Zucconi L, Onofri S, 2011 Resistance to UV-B induced DNA damage in extreme-tolerant cryptoendolithic Antarctic fungi: detection by PCR assays. *Fungal Biol* 115, 937-944. [PubMed: 21944205].
- (28) Francisco Solano.2020. Photoprotection and Skin Pigmentation: Melanin-Related Molecules and Some Other New Agents Obtained from Natural Sources. *Molecules*, 25, 1537; doi:10.3390.
- (29) Juzeniene, A.; Moan, J.2012. Beneficial effects of UV radiation other than via vitamin D production. *Dermatoendocrinol* , 4, 109-117.
- (30) Geoffrey, K.; Mwangi, A.N.; Maru, S.M. 2019.Sunscreen products: Rationale for use, formulation development and regulatory considerations. *Saudi Pharm. J.* 27, 1009-1018.
- (31) Cowley RE, Tian L, Solomon EI, 2016 Mechanism of O<sub>2</sub> activation and substrate hydroxylation in noncoupled binuclear copper monooxygenases. *Proc Natl Acad Sci U S A* 113, 12035-12040. [PubMed: 27790986].
- (32) Apte M., Girme G., Bankar A., RaviKumar A., injarde S. 2013. 3,4-dihydroxy-Lphenylalanine-derived melanin from *Yarrowia lipolytica* mediates the synthesis of silver and gold nanostructures. *Journal of Nanobiotechnology*, 11:2.
- (33) Olennikov DN, Tankhaeva LM, Rokhin AV, Agafonova SV. 2012.Physicochemical properties and antioxidant activity of melanin fractions from *Inonotus obliquus sclerotia*. *Chem Natural Compounds* 48:396-403. doi:10.1007/s10600-012-0260-y.
- (34) Abdelahad Khajo, Ruth A. Bryan, Matthew Friedman , Richard M. Burger , Yan Levitsky, Arturo Casadevall ,

- Richard S. Magliozzo Ekaterina Dadachova.2011. Protection of Melanized *Cryptococcus neoformans* from Lethal Dose Gamma Irradiation Involves Changes in Melanin's Chemical Structure and Paramagnetism. *PLoS ONE*. Volume 6 | Issue 9 | e25092
- (35) Na, J.-I.; Shin, J.-W.; Choi, H.-R.; Kwon, S.-H.; Park, K.C.2019. Resveratrol as a Multifunctional Topical Hypopigmenting Agent. *Int. J. Mol. Sci*, 20, 956.
- (36) Pillaiyar, T.; Namasivayam, V.; Manickam, M.; Jung, S.-H.2018. Inhibitors of Melanogenesis: An Updated Review. *J. Med. Chem*, 61, 7395-7418.
- (37) Arturo Solis Herrera .2016. The intrinsic chemistry of melanin modifies radically current concepts about the bioenergetics of photosynthesis. *Clin Res Trials*, V. 2(2): 147-152, doi: 10.15761/CRT.1000132.
- (38) Radames J.B. Cordero, Vincent Robert, Gianluigi Cardinali, Ebuka S. Arinze, Susanna M. Thon, and Arturo Casadevall.2018. Impact of Yeast Pigmentation on Heat Capture and Latitudinal Distribution. *Current Biology* 28, 2657-2664,
- (39) Dadachova, E.; Bryan, R.A.; Huang, X.; Moadel, T.; Schweitzer, A.D.; Aisen, P.; Nosanchuk, J.D.; Casadevall, A. Ionizing radiation changes the electronic properties of melanin and enhances the growth of melanized fungi. *PLoS ONE* 2007, 2, e457
- (40) Hao Jie WongNuradilla Mohamad-FauziMohammed Rizman-IdidPeter Conve , Siti Aisyah Alias .2019. Protective mechanisms and responses of micro-fungi towards ultraviolet-induced cellular damage. *Polar Science* 20 ; 19-34.
- (41) Solano, F. Melanins: 2014.Skin pigments and much more?types, structural models, biological functions, and formation routes. *New J. Sci.*, 1-28
- (42) Débora Lina Moreno Azócar, Marcelo Fabián Bonino, María Gabriela Perotti, James A. Schulte, , Cristian Simón Abdala and Félix Benjamín Cruz.2016. Effect of body mass and melanism on heat balance in *Liolaemus* lizards of the *goetschi* clade. *Journal of Experimental Biology*, 219, 1162-1171 doi:10.1242/jeb.129007
- (43) Nosanchuk, J.D.; Ovalle, R.; Casadevall, A.2001. Glyphosate inhibits melanization of *Cryptococcus neoformans* and prolongs survival of mice after systemic infection. *J. Infect. Dis*, 183, 1093-1099
- (44) Revskaya E, Chu P, Howell RC, Schweitzer AD, Bryan RA, Harris M, Gelfen G, Jiang Z, Jandl T, Kim K, Ting LM, Sellers RS, Dadachova E, Casadevall A, 2012 Compton scattering by internal shields based on melanin-containing mushrooms provides protection of gastrointestinal tract from ionizing radiation. *Cancer Biother Radiopharm* 27, 570-576. [PubMed: 23113595] .
- (45) Soares Bronze-Uhle E, Piacenti-Silva M, Paulin JV, Battocchio C, de Oliveira Graeff CF, 2015 Synthesis of water-soluble melanin. *ArXiv e-prints* 1508.07457
- (46) Hollinger, J.C.; Angra, K.; Halder, R.M. 2018. Are Natural Ingredients Effective

- tive in the Management of Hyperpigmentation? A Systematic Review. J. Clin. Aesthetic Dermatol, 11, 28-37.
- (47) Sandra R. Pombeiro-Sponchiado, Gabriela S. Sousa, Jazmina C. R. Andrade, Helen F. Lisboa and Rita C. R. Gonçalves. 2017. Production of Melanin Pigment by Fungi and Its Biotechnological Applications; <http://dx.doi.org/10.5772/67375>
- (48) Tudor D, Robinson SC, Cooper PA, 2012 The influence of moisture content variation on fungal pigment formation in spalted wood. AMB Express 2, 69. [PubMed: 23245292]
- (49) Akilandeswari P, Pradeep BV. 2016. Exploration of industrially important pigments from soil fungi. Appl Microbiol Biotechnol;100(4):1631-1643.
- (50) Mallique Qader M., Ahmed A. Hamed, Sylvia Soldatou, Mohamed Abdelraof, Mohamed E. Elawady, Ahmed S. I. Hassane, Lassaad Belbahri, Rainer Ebel and Mostafa E. Rateb. 2021. Antimicrobial and Antibiofilm Activities of the Fungal Metabolites Isolated from the Marine Endophytes *Epicoccum nigrum* M13 and *Alternaria alternata* 13A. Mar. Drugs, 19, 232
- (51) Soumya, K.; Narasimha Murthy, K.; Sreelatha, G.L.; Tirumale, S. 2018. Characterization of a red pigment from *Fusarium chlamydosporum* exhibiting selective cytotoxicity against human breast cancer MCF-7 cell lines. J. Appl. Microbiol, 125, 148-158.
- (52) Ajay C. Lagashetti, Laurent Dufossé, Sanjay K. Singh and Paras N. Singh. 2019. Fungal Pigments and Their Prospects in Different Industries. Microorganisms, 7, 604 <http://dx.doi.org/10.3390/7120604>.
- (53) Alfonso Blazquez-Castro and; Juan Carlos Stockert. 2021. Biomedical overview of melanin. 1. Updating melanin biology and chemistry, physico-chemical properties, melanoma tumors, and photothermal therapy. BIOCELL, 45(4): 849-862.
- (54) Rao, M.P.N.; Xiao, M.; Li, W.J. 2017. Fungal and bacterial pigments: Secondary metabolites with wide application. Front. Microbiol, 8, 1113.
- (55) Sumbal Sajid and Nukba Akbar. 2018. Applications of fungal pigments in biotechnology. Pure Appl. Biol., 7(3): 922-930, September, <http://dx.doi.org/10.19045/bspab.2018.700111>
- (56) Caro, Y.; Venkatachalam, M.; Lebeau, J.; Fouillaud, M.; Dufossé, L. 2017. Pigments and colorants from filamentous fungi. In Fungal Metabolites; Merillon, J.-M., Ramawat, K.G., Eds.; Springer International Publishing: Cham, Switzerland; pp. 499-568.



