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THE HIDDEN WORLD OF MARINE MELANIN PRODUCERS: A REVIEW OF RECENT ADVANCES

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ABSTRACT

Melanin, a high-molecular-weight biopolymer, plays a crucial role in biological systems due to its exceptional photoprotective, antioxidative and metal-binding properties. While traditionally sourced from fungi, plants, and mammals, marine-derived melanin has garnered significant attention due to its unique structural and functional characteristics. Marine bacteria, particularly extremophiles, have emerged as promising and sustainable sources of melanin, offering enhanced stability, tunable physicochemical properties, and eco-friendly biosynthesis pathways. This review explores the biosynthetic mechanisms of marine bacterial melanin, focusing on enzymatic pathways such as tyrosinase-mediated and polyketide synthase (PKS)-dependent processes. Furthermore, we highlight the diverse applications of melanin in biomedicine, environmental remediation, and advanced materials, with special emphasis on its potential in electronics and glass technology. The integration of melanin in bioelectronics, nanomaterials, and optical coatings underscores its versatility beyond conventional applications. Finally, we discuss current challenges and future prospects in scaling up microbial melanin production for industrial and commercial applications.

KEYWORDS: Marine bacterial melanin, biopolymer, tyrosinase, polyketide synthase, bioelectronics, bioremediation, nanomaterials, sustainable biotechnology.

1. INTRODUCTION

Melanin is a ubiquitous biopolymer known for its diverse physiological functions and unique physicochemical properties. It is primarily responsible for pigmentation in various organisms and plays a crucial role in photoprotection, metal chelation, and oxidative stress resistance. Structurally, melanin is categorized into four major types: eumelanin, pheomelanin, allomelanin, and pyomelanin. Eumelanin, the most abundant type, is a black-brown polymer derived from tyrosine oxidation, whereas pheomelanin, a red-yellow variant, incorporates sulfur-containing cysteine residues (d'Ischia et al., 2013). Allomelanin, typically found in fungi and plants, is synthesized via polyketide pathways rather than tyrosine metabolism, while pyomelanin is a byproduct of homogentisic acid polymerization, commonly produced by bacteria (Nosanchuk et al., 2015).

Beyond pigmentation, melanin exhibits remarkable functional properties. It provides UV protection by absorbing and dissipating harmful radiation, thus preventing cellular damage (Solano, 2020). Additionally, melanin acts as a potent antioxidant and free radical scavenger, contributing to cellular defense mechanisms in various microorganisms (Plonka & Grabacka, 2006). Its ability to bind heavy metals and toxins makes it a promising candidate for bioremediation applications (Zhang et al., 2021).

1.1 Uniqueness of Marine Bacterial Melanin

Marine bacteria have evolved to produce melanin as a survival strategy, particularly in response to extreme environmental conditions such as high salinity, temperature fluctuations, and intense UV radiation (Sanchez et al., 2022). Unlike their terrestrial counterparts, marine-derived melanin exhibits enhanced stability and distinct structural modifications, which contribute to its superior antioxidant and metal-chelating capabilities. This adaptation is particularly advantageous in deep-sea environments, where organisms are exposed to high pressure and oxidative stress (Ravanat et al., 2020).

Comparative studies suggest that marine bacterial melanin differs from fungal and terrestrial bacterial melanin in terms of molecular composition and biosynthetic pathways (Guo et al., 2019). For instance, while fungal melanin is predominantly synthesized via the dihydroxyphenylalanine (DOPA) pathway, marine bacteria often utilize polyketide synthase (PKS)-mediated routes, leading to structurally diverse melanin variants with enhanced physicochemical stability (Fang et al., 2021). Furthermore, marine melanin demonstrates superior solubility and bioactivity, making it an attractive candidate for various biomedical and industrial applications (Subash et al., 2023).

Given its unique biochemical attributes, marine bacterial melanin is emerging as a promising material for applications ranging from bioelectronics to environmental remediation. The subsequent sections of this review explore its biosynthetic pathways, functional properties, and innovative applications across multiple industries.

2. Biosynthetic Pathways and Enzymes Involved

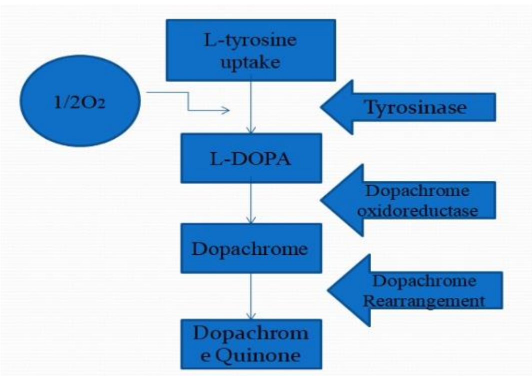
2.1 General Pathways for Melanin Biosynthesis

Melanin biosynthesis in bacteria predominantly occurs through two primary pathways: the tyrosinase-dependent pathway and the polyketide synthase (PKS) pathway.

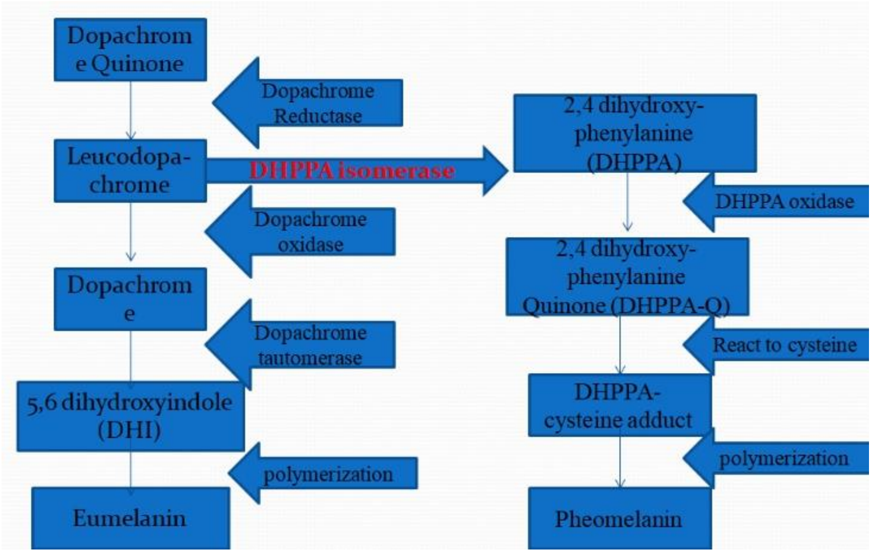
Tyrosinase-Dependent Pathway (L-DOPA to Melanin)

In this pathway, the enzyme tyrosinase catalyses the oxidation of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA), which is subsequently oxidized to dopaquinone. Dopaquinone undergoes a series of non-enzymatic reactions leading to the formation of dopachrome, which eventually polymerizes into melanin. The key steps are as follows:

- **Oxidation of L-tyrosine to L-DOPA:** Tyrosinase hydroxylates L-tyrosine to form L-DOPA.
- **Oxidation of L-DOPA to dopaquinone:** Tyrosinase further oxidizes L-DOPA to dopaquinone.
- **Formation of dopachrome: Dopaquinone** undergoes intramolecular cyclization to form dopachrome.
- **Polymerization to melanin:** Dopachrome spontaneously polymerizes through a series of oxidation and rearrangement reactions, resulting in melanin formation.



(Fig: a) Uptake of tyrosine and conversion to dopachrome Quinone.



(Fig: b)

If dopachrome reductase is present then it will convert Dopachrome quinone to leucodopachrome and further to producing pheomelanin if it is absent then it will convert to Dopachrome and then to DHI by tautomerase then polymerization to form eumelanin).

This pathway is common in various microorganisms, including certain marine bacteria.

Polyketide Synthase (PKS) Pathway in Bacteria

The PKS pathway involves the assembly of melanin precursors through the action of polyketide synthases. These enzymes catalyse the condensation of malonyl-CoA units to form a polyketide chain, which undergoes cyclization and oxidation to yield melanin. The steps include:

- **Initiation**: Polyketide synthase initiates the condensation of malonyl-CoA units.
- **Chain elongation:** Sequential addition of malonyl-CoA extends the polyketide chain.
- **Cyclization and aromatization**: The elongated chain undergoes cyclization and aromatization to form a phenolic structure.
- **Oxidation and polymerization:** The phenolic intermediates are oxidized and polymerized to produce melanin.
- This pathway is notably present in certain bacterial species, contributing to the structural diversity of bacterial melanins.

2.2 Enzymes Involved in Marine Bacterial Melanin Production

Marine bacteria utilize specific enzymes for melanin production, primarily tyrosinase, laccase, and polyketide synthase.

Tyrosinase

Tyrosinase is a copper-containing enzyme that catalyses the ortho-hydroxylation of monophenols to o-diphenols and the subsequent oxidation to o-quinones, leading to melanin formation. In marine bacteria, tyrosinase activity is crucial for melanin biosynthesis via the L-DOPA pathway. The regulation of tyrosinase expression is influenced by environmental factors such as nutrient availability and stress conditions.

Laccase

Laccase is a multi-copper oxidase that oxidizes a broad range of phenolic and non-phenolic substrates, facilitating melanin synthesis. In marine bacteria, laccase contributes to the polymerization of phenolic intermediates into melanin. The expression of laccase is often regulated by environmental cues, enabling bacteria to adapt to changing conditions.

Polyketide Synthase

Polyketide synthases are multifunctional enzymes that assemble polyketide chains from acyl-CoA precursors. In marine bacteria, PKS enzymes catalyse the formation of melanin precursors through iterative condensation reactions. The genetic regulation of PKS involves complex networks that respond to environmental signals, ensuring efficient melanin production under appropriate conditions.

Case Studies: Pseudomonas, Bacillus, and Staphylococcus Species

Pseudomonas: Certain Pseudomonas species produce pyomelanin via the homogentisate pathway, involving the accumulation and polymerization of homogentisic acid. This process is linked to the degradation of aromatic amino acids and is regulated by genes encoding enzymes such as 4-hydroxyphenylpyruvate dioxygenase.

Bacillus: *Bacillus species* utilize the tyrosinase-dependent pathway for melanin production. The expression of tyrosinase in these bacteria is regulated by environmental factors and contributes to stress resistance.

Staphylococcus: *Staphylococcus species* produce melanin through the activity of oxidoreductases like tyrosinase and laccase. Melanin production in these bacteria is associated with increased resistance to oxidative stress and host immune responses.

2.3 Genetic and Metabolic Engineering for High-Yield Melanin Production

Advancements in genetic and metabolic engineering have significantly enhanced melanin production in marine bacteria. Techniques such as CRISPR-Cas9-mediated genome editing and pathway optimization have been pivotal in increasing yield and efficiency.

CRISPR-Cas9 and Genetic Modifications

The CRISPR-Cas9 system has revolutionized genome editing, allowing precise modifications in bacterial genomes. In marine-derived fungi, CRISPR-Cas9 has been employed to delete or overexpress genes involved in melanin biosynthesis, thereby optimizing production pathways. For instance, novel CRISPR-based tools have been developed to enhance metabolic engineering capabilities, enabling efficient production of specialized metabolites, including pigments like melanin.

Metabolic Pathway Optimization

Beyond genetic editing, metabolic engineering strategies have been applied to redirect carbon flux towards melanin synthesis. By manipulating central metabolic pathways, researchers have increased the availability of precursors necessary for melanin production. For example, advances in metabolic engineering have simplified the transfer of biosynthetic pathways from natural sources to production hosts, facilitating the efficient production of complex molecules like melanin.

Case Study: *Vibrio natriegens*

The marine bacterium *Vibrio natriegens*, known for its rapid growth rate, has been genetically engineered to produce melanin efficiently. By expressing a heterologous tyrosinase gene, researchers achieved melanin yields of up to 7.57 g/L, with a volumetric productivity of 473 mg L^{-1} h^{-1} and a 100% conversion rate in an optimized medium.

Implications and Future Directions

The integration of CRISPR-Cas9 and metabolic engineering holds significant potential for industrial-scale melanin production. These methodologies enable precise control over biosynthetic pathways, leading to higher yields and cost-effective processes. Future research may focus on refining these techniques and exploring their applications across diverse marine bacterial species to fully harness their potential in melanin biosynthesis.

3. Applications in Various Fields

3.1 Biomedical and Pharmaceutical Applications

Bacterial melanin has gained immense attention in biomedical and pharmaceutical applications due to its antioxidant, antimicrobial, UV-protective, wound-healing, and drug-delivery properties. Its biocompatibility, biodegradability, and multifunctionality make it a promising material for healthcare applications.

Antioxidant and Antimicrobial Properties

Melanin as a Natural Antioxidant

Melanin exhibits potent free radical scavenging activity, protecting cells from oxidative stress and DNA damage caused by reactive oxygen species (ROS) (Zhang et al., 2021). The antioxidant potential of bacterial melanin has been explored for neuroprotection, cancer therapy, and aging-related disorders (Gómez & Nosanchuk, 2020).

Photothermal Antimicrobial Applications

Melanin nanoparticles generate localized heat upon near-infrared (NIR) light exposure, effectively killing bacteria and biofilms (Wu et al., 2022). Pseudomonas aeruginosa-derived melanin has been found to inhibit bacterial and fungal growth, making it a potential natural antimicrobial agent (Banerjee et al., 2019).

Melanin exhibits notable antioxidant capabilities, effectively scavenging free radicals and protecting cells from oxidative stress. This property is particularly beneficial in mitigating UV-induced DNA damage in skin cells. Additionally, melanin's photothermal properties have been harnessed for antimicrobial applications. Upon near-infrared irradiation, melanin generates localized heat, leading to the eradication of bacteria, making it a promising agent in combating microbial infections.

UV Protection and Wound Healing Applications

Due to its ability to absorb and dissipate ultraviolet (UV) radiation, bacterial melanin has been explored in natural sunscreens and skin protection formulations (Singh et al., 2021). Melanin-containing skincare formulations reduce the risk of UV-induced skin aging and skin cancer (Patel et al., 2022).

In wound healing, melanin-integrated hydrogels have demonstrated enhanced therapeutic outcomes. These hydrogels, when applied to wounds, exhibit photothermal antibacterial and antioxidant properties, accelerating the healing process. Moreover, the application of synthetic melanin particles has been shown to decrease edema, reduce eschar detachment time, and increase the rate of wound area reduction in injury models.

Bacillus and Pseudomonas-derived melanin enhances collagen synthesis and fibroblast proliferation, promoting wound healing (García-Rubio et al., 2020). Melanin-loaded hydrogel dressings have demonstrated enhanced healing rates and reduced infection risks in burn wounds (Yuan et al., 2023).

Drug Delivery Systems and Biocompatibility

The biocompatibility of melanin makes it an excellent candidate for drug delivery systems. Melanin-like nanoparticles can serve as carriers for therapeutic agents, offering controlled release profiles and enhanced stability. For instance, polydopamine-coated insulin particles have demonstrated pH-responsive insulin release, ensuring sustained delivery under physiological conditions. Additionally, melanin coatings on various substrates have been shown to improve cell attachment and proliferation, underscoring their potential in regenerative medicine applications.

Melanin nanoparticles (MNPs) are being developed for targeted drug delivery systems, ensuring controlled and sustained release of therapeutic compounds (Chakraborty et al., 2020). Polydopamine-coated melanin nanoparticles improve drug stability and bioavailability, enhancing their potential in cancer therapy (Ahmed et al., 2021).

Applications in Cancer Therapy

Melanin-based nanoparticles have shown promise in photothermal therapy (PTT) and photodynamic therapy (PDT) for cancer treatment (Xie et al., 2023). Bacterial melanin has been used to encapsulate chemotherapy drugs, reducing their toxicity and improving their therapeutic index (Li et al., 2022).

In summary, bacterial melanin's multifunctional properties position it as a valuable biomaterial in various biomedical and pharmaceutical applications, from serving as an antioxidant and antimicrobial agent to enhancing drug delivery systems and promoting tissue regeneration.

3.2 Environmental and Industrial Applications

Bacterial melanin has gained considerable attention for its role in environmental sustainability, particularly in heavy metal detoxification, bioremediation, wastewater treatment, and pollutant removal. Its unique chemical structure, including carboxyl, hydroxyl, and amine groups, allows it to chelate and adsorb various contaminants effectively.

Heavy Metal Detoxification and Bioremediation

Melanin as a Natural Heavy Metal Chelator

Bacterial melanin contains functional groups that can bind to toxic metals like lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg), reducing their bioavailability in contaminated environments (El-Naggar et al., 2020). The high-affinity binding sites on melanin surfaces enable it to act as a natural detoxifying agent (Banerjee et al., 2021).

Microbial Bioremediation Potential

Several melanin-producing bacteria, including *Pseudomonas*, *Bacillus*, and *Streptomyces species*, have demonstrated the ability to remediate heavy metal-contaminated soils and water (Kumar et al., 2019). Studies highlight melanin-based biofilms as effective in metal immobilization, preventing further spread of contaminants (Singh et al., 2022).

Case Study: Chromium (Cr) Removal

Melanin extracted from Pseudomonas putida showed an 80% reduction in Cr (VI) toxicity, emphasizing its application in Cr-contaminated wastewater treatment (Shivakumar et al., 2023).

Role in Wastewater Treatment and Pollutant Removal

Melanin in Industrial Wastewater Treatment

Melanin-based nanoparticles can adsorb organic pollutants such as dyes, pesticides, and pharmaceutical residues from wastewater (Gao et al., 2022). Studies show bacterial melanin-coated membranes enhance water filtration by preventing biofouling (Zhou et al., 2021).

Removal of Organic Pollutants

Melanin-containing hydrogels have shown high efficiency in removing endocrine-disrupting chemicals (EDCs) like bisphenol A (BPA) from water (Li et al., 2023). Polydopamine-coated melanin nanospheres have been explored for selective adsorption of pharmaceutical pollutants like antibiotics and hormones (Ahmed et al., 2020).

Application in Oil Spill Cleanup

Melanin-rich bacterial biofilms have been tested for degrading petroleum hydrocarbons, showing promise for oil spill remediation in marine environments (Wang et al., 2023).

3.3 Cosmetic and Food Industry Applications

Melanin, a natural pigment synthesized by various organisms, has garnered significant attention in both the cosmetic and food industries due to its unique properties.

Cosmetic Applications

- **Hair Dyes:** Melanin's natural pigmentation properties have been explored for use in hair dye formulations. Research indicates that melanin pigments can be utilized in cosmetics, including hair dyes, providing a natural alternative to synthetic colorants.
- **Skincare Products**: Melanin's ability to absorb ultraviolet (UV) radiation makes it a valuable ingredient in skincare products aimed at photoprotection. Its antioxidant properties further enhance its appeal, offering protection against oxidative stress. Studies have highlighted melanin's potential in the cosmetic industry, particularly in products such as sunscreen and hair dyes.

Food Industry Applications

- **Natural Colorant:** Melanin can serve as a natural food colorant, providing hues ranging from brown to black. Its high safety profile and low toxicity make it an attractive alternative to synthetic colorants. Research has demonstrated that melanin extracted from date fruits can be utilized as a functional ingredient in foods, offering a natural colouring option.
- **Antioxidant and Preservative:** Beyond its colouring properties, melanin exhibits strong antioxidant activity, which can enhance the shelf life of food products by preventing oxidative spoilage. Its incorporation into food packaging materials has been explored to leverage its antibacterial and antioxidant properties, contributing to food preservation. Studies have shown that melanin possesses anti-biofilm properties, suggesting its potential as a food preservative if proven to be non-toxic

3.4 Role of Melanin in Electronics and Bio-Nanotechnology

Melanin, beyond its biological role as a pigment, has emerged as a material of interest in electronics and bio-nanotechnology due to its unique electrical properties and biocompatibility.

Melanin as an Organic Semiconductor

Melanin exhibits semiconductive properties, enabling both electronic and ionic conductivity. This dual conductivity is influenced by factors such as hydration levels and structural organization. Studies have reported conductivity values ranging from 10^{-5} to 10^{-13} S/cm, depending on the hydration state of the biopolymer. These properties position melanin as a potential material for organic semiconductors, with applications in electronic devices that require both charge transport and storage capabilities.

Use in Bioelectronics and Nanodevices

The biocompatibility and flexibility of melanin make it suitable for integration into bioelectronic devices. Its ability to conduct protons and electrons has been leveraged in the development of biosensors and flexible electronics. For instance, melanin-based electrodes have been explored for use in aqueous sodium-ion batteries, demonstrating the material's potential in energy storage applications. Additionally, melanin's broad-spectrum light absorption has been utilized in photovoltaic devices, highlighting its versatility in nanodevice applications.

Potential for Biocompatible Electronic Implants

The inherent biocompatibility of melanin, coupled with its electrical properties, makes it a promising candidate for electronic implants. Research has demonstrated that melanin can be synthesized rapidly, facilitating its use in bioelectronic devices. Moreover, melanin's properties have been harnessed in the development of flexible and stretchable bioelectronic devices, which can conform to biological tissues and maintain electrical integrity under deformation. These characteristics are crucial for the development of implants that can seamlessly integrate with human tissues, reducing the risk of rejection and improving device performance.

In summary, melanin's unique combination of electrical conductivity, flexibility, and biocompatibility positions it as a valuable material in the fields of electronics and bio-nanotechnology. Ongoing research continues to uncover new applications, paving the way for innovative devices that leverage the multifunctional properties of this natural pigment.

3.5 Applications of Melanin in Glass Technology

Melanin, a natural pigment renowned for its broad-spectrum light absorption and photoprotective properties, has been explored for various applications in glass technology. Below is a detailed examination of its potential roles:

3.5.1. Optical Properties and UV-Filtering Capabilities in Glass Manufacturing

Melanin's inherent ability to absorb ultraviolet (UV) radiation makes it a promising additive in glass manufacturing to enhance UV protection. Studies have shown that incorporating melanin nanoparticles into polymer matrices can significantly block UV light, with even a 1 wt % melanin loading effectively absorbing most UV radiation below 340 nm. This characteristic suggests that melanin-infused glass could serve as an effective UV filter, protecting interiors from harmful UV exposure without compromising visible light transmission.

3.5.2. Potential Use in Smart Glass and Protective Coatings

The unique optical properties of melanin have been harnessed in the development of smart glass technologies and protective coatings:

Smart Glass: Melanin-infused eyewear demonstrates the material's capacity to filter out high-energy visible (HEV) light and provide superior protection from UVA/UVB radiation, reducing the risk of cataracts and macular degeneration. This principle can be extended to architectural applications, where melanin-infused glass could dynamically adjust light transmission properties in response to environmental conditions, thereby enhancing energy efficiency and occupant comfort.

Protective Coatings: Bioinspired coatings incorporating melanin-like materials have been developed to enhance the durability and functionality of glass surfaces. These coatings exhibit superior UV protection, meeting long-term service conditions under outdoor sunlight, and contribute to personal thermal management and anti-icing/deicing properties. Such multifunctional coatings can extend the lifespan of glass products and reduce maintenance requirements.

3.5.3. Bioinspired Glass Materials Incorporating Melanin for Enhanced Durability

Drawing inspiration from natural systems, researchers have explored the integration of melanin and melanin-like materials into glass to enhance durability:

Self-Healing Properties: Melanin-like coatings have been observed to endow materials with self-healing properties, allowing them to repair themselves in case of damage. This capability extends the durability of the materials and improves their resistance to environmental factors.

Structural Enhancements: Incorporating melanin into polymer blends has been shown to enhance optical conductivity, suggesting potential applications in developing glass materials with improved mechanical and optical properties.

4. Conclusion and Future Prospects

Melanin, a natural pigment synthesized by various organisms, has garnered significant attention due to its diverse industrial applications, including in cosmetics, food preservation, electronics, and bio-nanotechnology. Marine bacteria have emerged as promising sources for melanin production, offering potential advantages in sustainability and efficiency. Below is a summary of key findings, challenges in large-scale production, and future research directions.

Summary of Key Findings

Diverse Applications: Melanin's unique properties have led to its exploration in various industries. In cosmetics, it serves as a natural pigment for hair dyes and skincare products. In the food industry, melanin functions as an antioxidant and stabilizer, aiding in preservation. Additionally, its role as an organic semiconductor has opened avenues in electronics and bio-nanotechnology, including applications in biosensors and flexible electronics.

Marine Bacterial Melanin Production: Marine bacteria have been identified as efficient producers of melanin. For instance, the fast-growing marine bacterium *Vibrio natriegens* has been genetically engineered to synthesize melanin rapidly, achieving production rates faster than previously reported heterologous systems.

Challenges in Large-Scale Production of Marine Bacterial Melanin

Extraction and Purification: Melanin's insolubility in most solvents poses significant challenges in its extraction and purification processes, hindering cost-effective large-scale production.

Production Efficiency: While marine bacteria like *V. natriegens* offer rapid growth, optimizing melanin yields remains a challenge. Factors such as the choice of melanin-producing enzymes and the metabolic pathways utilized can significantly impact production efficiency.

Process Optimization: Achieving high-titer melanin production requires meticulous optimization of physiological and nutritional parameters. Implementing efficient optimization methods is crucial to enhance microbial growth and melanin synthesis.

Future Research Directions

Genetic Engineering: Advancements in genetic engineering can facilitate the development of marine bacterial strains with enhanced melanin production capabilities. By manipulating metabolic pathways and regulatory networks, researchers can improve yield and efficiency.

Industrial Applications: Expanding the applications of melanin in various industries necessitates the development of cost-effective and scalable production methods. Innovations in bioprocessing and microbial fermentation can contribute to this goal.

Sustainable Production: Focusing on sustainable and renewable feedstocks for melanin production aligns with global efforts toward environmental sustainability. Utilizing marine bacteria offers a promising approach, given their rapid growth rates and the abundance of marine resources.

In conclusion, while marine bacterial melanin holds significant promise for various industrial applications, addressing the challenges in large-scale production is essential. Future research should focus on genetic enhancements, process optimization, and sustainable practices to fully realize the potential of marine bacterial melanin.

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