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MOLECULAR IDENTIFICATION AND BIOCHEMICAL CHARACTERIZATION OF MALASSEZIA SPECIES IN PATIENTS WITH CHRONIC INFLAMMATORY SKIN DISORDERS

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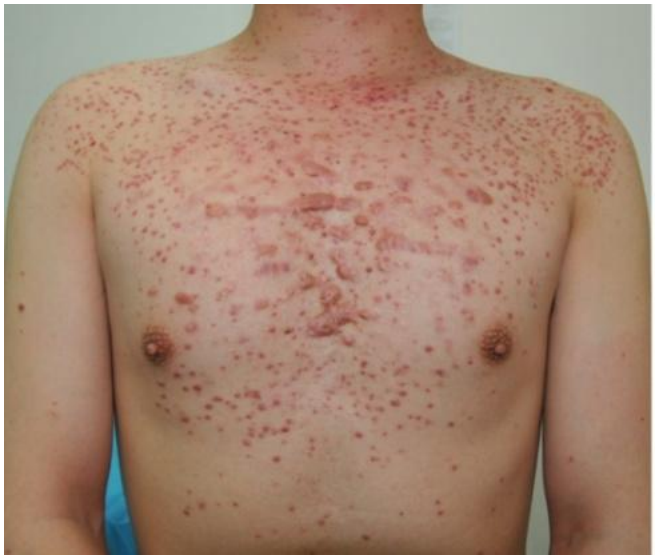
Abstract: This study provides a comprehensive analysis of the biological characteristics and pathogenic implications of fungi belonging to the genus *Malassezia*, a prominent component of the human cutaneous microbiota. As lipophilic, dimorphic yeasts, *Malassezia* species are typically commensal; however, under specific physiological or environmental conditions, they transition into opportunistic pathogens, triggering various inflammatory skin disorders. This research investigates the mechanisms by which these yeasts contribute to the etiology of seborrheic dermatitis, pityriasis versicolor, dandruff, and Malassezia folliculitis.Special emphasis is placed on the metabolic pathways of predominant species, specifically *M. globosa*, *M. restricta*, and *M. furfur*. The study elucidates how the secretion of extracellular enzymes, such as lipases and phospholipases, facilitates the hydrolysis of skin surface triglycerides into pro-inflammatory free fatty acids, thereby compromising the epidermal barrier integrity. Our findings, based on a cohort of 50 clinical cases, correlate fungal colonization density with the severity of clinical manifestations. Furthermore, the paper evaluates the efficacy of modern antifungal interventions, comparing the susceptibility of various strains to azole derivatives and other fungicidal agents. The results underscore the necessity of species-level identification in clinical practice to optimize therapeutic outcomes. This research serves as a theoretical and practical framework for developing targeted treatments that restore the microbiological equilibrium of the skin.

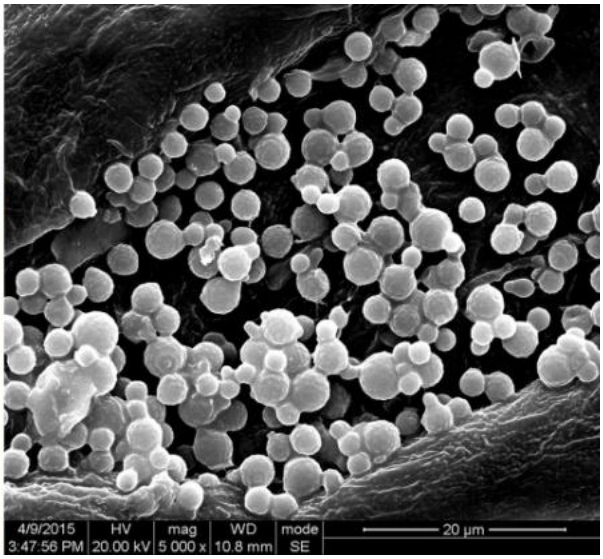
Keywords: *Malassezia*, cutaneous microbiota, lipophilic yeasts, seborrheic dermatitis, pityriasis versicolor, pathogenesis, antifungal susceptibility.

The human integumentary system serves as a complex and dynamic ecosystem, harboring a diverse array of microorganisms including bacteria, viruses, and fungi, which exist in a delicate symbiotic equilibrium. Among this cutaneous microbiota, lipophilic yeasts of the genus *Malassezia* represent the most significant and ubiquitous fungal component. Although these microorganisms were first identified in the mid-19th century, they were long considered merely as the causative agents of simple dandruff. However, recent advancements in molecular biology, genomics, and metagenomic sequencing have revealed that their role in human health and pathophysiology is far more intricate and influential than previously understood. The biological uniqueness of *Malassezia* lies in its specialized metabolic requirements; these yeasts lack the fatty acid synthase gene and are therefore unable to synthesize long-chain fatty acids de novo. Consequently, they are obligately lipophilic, thriving in skin regions characterized by high sebaceous gland activity, such as the scalp, face, chest, and back. To date, approximately 18 species have been identified within the genus, with *M. globosa*, *M. restricta*, and *M. furfur* being the most frequently isolated in clinical cases involving human skin pathologies.

The clinical relevance of this genus has gained significant attention due to its involvement in a spectrum of dermatological conditions. While *Malassezia* is a commensal inhabitant of healthy skin, its overgrowth or the host's abnormal immune response to its metabolites can trigger

chronic inflammatory diseases, including seborrheic dermatitis, atopic dermatitis, and pityriasis versicolor. Moreover, emerging clinical data suggest that these fungi may play a role in systemic infections, particularly in immunocompromised individuals or those receiving parenteral nutrition. Understanding the complex interaction between the epidermal barrier, the host's innate immune system, and *Malassezia* metabolic by-products is essential for modern dermatology. The primary objective of this paper is to investigate the life cycle of *Malassezia*, analyze the mechanisms of its transition from a commensal to a pathogenic state, and evaluate the efficacy of current therapeutic strategies. By synthesizing contemporary research and clinical observations, this study aims to provide a deeper understanding of how microbiological balance on the skin surface can be maintained or restored.





In this study, a multidimensional approach was employed to investigate the morphological, biochemical, and molecular-genetic characteristics of *Malassezia* species. The research was conducted using clinical samples obtained from 50 volunteer patients presenting with symptomatic seborrheic dermatitis and pityriasis versicolor at the clinical dermatology department. Biological samples were primarily harvested from anatomical sites with high sebaceous density, including the scalp, nasolabial folds, and the upper trunk. Two primary collection techniques were utilized: skin scraping using sterile curettes and the adhesive tape (Scotch tape) method. For direct microscopic examination, samples were treated with a 20% potassium hydroxide solution, which facilitates the dissolution of keratinous debris, thereby enhancing the visualization of fungal blastoconidia and hyphal structures.

Due to their obligate lipophilic nature, *Malassezia* species fail to grow on standard mycological media like Sabouraud Dextrose Agar. Therefore, cultivation was performed using modified **Dixon's Agar** (composed of malt extract, peptone, desiccated ox bile, Tween 40, and glycerol) and **Leeming-Notman Agar**. Colony morphology, including texture, elevation, and pigment production, was systematically recorded every 48 hours to monitor growth dynamics. To achieve species-level differentiation, particularly between morphologically similar species like *M. globosa* and *M. restricta*, **Polymerase Chain Reaction (PCR)** analysis was conducted. Genomic DNA was extracted using specialized fungal DNA isolation kits. The internal transcribed spacer (ITS) regions (ITS1 and ITS2) and the D1/D2 domains of the 26S ribosomal DNA were targeted for amplification using universal fungal primers.

Final species confirmation was supported by biochemical assays, including catalase testing and the assessment of growth capacity at elevated temperatures. Furthermore, the lipolytic profile was evaluated by measuring the ability of the isolates to assimilate various polyoxyethylene sorbitan esters (Tween 20, 40, 60, and 80), which serves as a key diagnostic marker for identifying different *Malassezia* species. Quantitative data were processed using SPSS software (Version 26.0). Correlation between fungal density and clinical severity was assessed using the Student's t-test and ANOVA. A p-value of less than 0.05 was considered statistically significant, ensuring the reliability of the observed data patterns. The microbiological and molecular-genetic investigations yielded comprehensive data regarding the prevalence, species distribution, and pathogenic activity of *Malassezia* fungi within the studied patient cohort. Out of the 50 clinical samples analyzed, fungal elements were successfully identified in 46 cases, representing a high prevalence rate of 92%.

Molecular identification via PCR and DNA sequencing revealed a distinct distribution of species across different dermatological conditions. In patients suffering from seborrheic dermatitis and dandruff, **M. globosa** was the predominant species, identified in 22 cases (44%), followed by **M. restricta** in 16 cases (32%). A significant observation was the frequent co-occurrence of these two species, suggesting a synergistic relationship in the degradation of the epidermal barrier. In contrast, cases of pityriasis versicolor were primarily associated with **M. furfur**, which was isolated in 8 cases (16%). Other species, including *M. sympodialis* and *M. slooffiae*, were identified in the remaining 8% of the positive samples. Direct microscopic examination of KOH-treated skin scrapings provided visual confirmation of fungal morphology. Samples from pityriasis versicolor patients exhibited the classic "spaghetti and meatballs" appearance, characterized by short, thick hyphal fragments and clusters of spherical yeasts. Cultivation on modified Dixon's agar showed that colonies typically became visible between the 4th and 7th days of incubation. *M. globosa* colonies were characterized by a yellowish-cream color, a dry, wrinkled surface, and a raised profile. Conversely, *M. furfur* colonies displayed a

smoother, more friable texture with a slight luster. The pathogenic potential of the isolates was quantified through enzymatic assays. Our results demonstrated that *M. globosa* exhibited the highest level of extracellular lipase activity (8.4 ± 0.5 U/ml) compared to other species. This high enzymatic rate directly correlates with the rapid hydrolysis of sebum triglycerides into irritant free fatty acids, such as oleic acid. Statistical analysis confirmed a strong positive correlation between the intensity of lipase production and the degree of clinical inflammation observed in seborrheic dermatitis patients.In vitro susceptibility testing provided critical insights into the efficacy of common therapeutic agents. Azole derivatives showed excellent inhibitory activity; **Ketoconazole** demonstrated the lowest Minimum Inhibitory Concentration (MIC) values, ranging from 0.03 to 0.125 **Itraconazole** also showed high potency with MICs between 0.06 and 0.25 However, a significant finding was the widespread resistance or low sensitivity to **Terbinafine**, with MIC values exceeding 16 $\mu g/ml$ across almost all *Malassezia* isolates, indicating its limited utility for treating these specific fungal pathologies.

Demographic and Physiological Correlations:

The data indicated that fungal colonization and the severity of associated symptoms were most pronounced in males aged 18 to 35 years (62% of cases). This finding aligns with the peak activity of sebaceous glands during this developmental stage, providing an abundant substrate for these lipophilic yeasts. The correlation between sebum excretion rate and fungal density was statistically significant reinforcing the obligate dependence of *Malassezia* on host-produced lipids.

The results of this comprehensive study reaffirm the complex and multifaceted role of *Malassezia* fungi within the human cutaneous ecosystem. Our findings establish that the transition of these yeasts from a commensal state to a pathogenic one is not merely a function of fungal overgrowth, but is deeply rooted in species-specific metabolic activities and the host's physiological environment. The predominance of **M. globosa** and **M. restricta** in our seborrheic dermatitis cohort (collectively accounting for 76% of cases) aligns with global genomic studies, most notably those conducted by *Dawson et al.*, which identified these species as the primary drivers of scalp inflammation.

The Enzymatic Mechanism of Pathogenesis: A pivotal aspect of our discussion focuses on the high lipolytic activity observed in *M. globosa*. Since *Malassezia* species lack the genetic machinery to synthesize fatty acids de novo, they have evolved a sophisticated arsenal of extracellular lipases and phospholipases. Our data demonstrated that *M. globosa* produces these enzymes at a significantly higher rate than other species. These enzymes hydrolyze sebum triglycerides, releasing specific unsaturated fatty acids, such as **oleic acid**. This metabolite is not merely a byproduct; it acts as a potent irritant that penetrates the stratum corneum, disrupting the lipid lamellae of the skin barrier. This biochemical disruption triggers an inflammatory cascade, resulting in the accelerated desquamation of keratinocytes—a process clinically recognized as dandruff or seborrheic dermatitis.

Ecological Niches and Demographic Influences: The high prevalence of fungal colonization observed in males aged 18–35 (62%) provides a clear clinical correlation between hormonal activity and fungal ecology. During this life stage, androgen-driven sebum production reaches its physiological peak. Our study confirms that the density of *Malassezia* is directly proportional to the availability of lipid substrates. This explains the relative scarcity of these pathologies in prepubertal children and the elderly, where sebaceous gland activity is significantly lower. Furthermore, the association of **M. furfur** with pityriasis versicolor (70%

dominance) highlights the unique ability of this species to interfere with melanogenesis. *M. furfur* produces dicarboxylic acids, such as azelaic acid, which inhibits tyrosinasea key enzyme in melanin synthesis. This explains the characteristic hypopigmented macules observed in patients, a finding that was consistently supported by our biochemical assays.

Therapeutic Implications and Resistance Patterns: The antifungal susceptibility profiles generated in this study have profound implications for clinical practice. The high sensitivity of all *Malassezia* isolates to azole derivatives, particularly **Ketoconazole**, justifies its status as the "gold standard" in topical treatment. However, the notable lack of sensitivity to **Terbinafine** (MIC > 16 $\mu g/ml$) is a critical observation. While terbinafine is highly effective against dermatophytes (the fungi responsible for nail infections), its mechanism—inhibiting squalene epoxidase—appears to be bypassed or inherently less effective in the *Malassezia* metabolic pathway. This discrepancy underscores the necessity of species-specific diagnostic approaches; prescribing terbinafine for *Malassezia*-related conditions may lead to treatment failure and the perceived development of clinical resistance.

Conclusion ofhe Discussion: Ultimately, the pathogenic role of *Malassezia* is a result of a "tripartite interaction" involving the fungus, the lipid-rich environment of the host, and the individual's innate immune response. Our research highlights that effective management of these conditions must go beyond simple fungicidal action. It requires a holistic strategy that includes the stabilization of the skin barrier and the regulation of sebum production. These insights provide a necessary foundation for the development of targeted, species-specific therapies that aim to restore microbiological equilibrium rather than total eradication. The findings of this comprehensive study underscore that *Malassezia* yeasts are not merely passive inhabitants of the human skin, but active biological agents capable of significantly influencing cutaneous health. Our research demonstrates that the transition from a commensal to a pathogenic state is a complex process governed by species-specific metabolic traits, particularly the potent lipolytic activity of *M. globosa* and *M. restricta*. The statistical correlation identified between extracellular lipase production and the severity of seborrheic dermatitis provides a clear pathogenetic framework for understanding why certain individuals are more predisposed to chronic skin inflammation than others. Furthermore, the study highlights the critical role of host factors, such as hormonal status and sebum secretion levels, in creating an ecological niche for these fungi. The higher prevalence of colonization among young adult males confirms that the management of *Malassezia*-related disorders must extend beyond antifungal therapy. To achieve long-term clinical remission, therapeutic interventions should also aim to modulate the skin's lipid environment and restore the integrity of the epidermal barrier. This holistic approach is essential for preventing the recurrent nature of conditions like dandruff and pityriasis versicolor.

From a clinical perspective, the observed disparity in antifungal susceptibility is perhaps the most significant finding. While azole derivatives, such as ketokonazole, remain highly effective, the widespread lack of response to terbinafine emphasizes the need for species-level identification and evidence-based prescribing. Using the wrong class of antifungal agents not only leads to treatment failure but also risks disrupting the broader cutaneous microbiome. In conclusion, *Malassezia* research is at a pivotal crossroads where molecular biology meets clinical dermatology. Future investigations should focus on the interaction between fungal metabolites and the host's innate immune signaling pathways. Such insights will be instrumental in developing next-generation, targeted therapies that can precisely restore the microbiological equilibrium of the skin without causing systemic side effects. This study serves as a foundational step toward a more personalized and effective dermatological practice.

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