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PHOTODYNAMIC INACTIVATION AGAINST THE CRITICAL PRIORITY PATHOGEN *Candida auris*

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Fungal pathogens and their associated infections present a growing challenge to global public health. Among these pathogens, *Candida auris* has emerged as a highly hazardous hospital-acquired microorganism, included in the critical priority group by the World Health Organization. Methylene Blue (MB) is a widely acknowledged photosensitizer utilized in antifungal photodynamic inactivation (PDI) and holds significant clinical applications. The MB methylation results in the formation of a more lipophilic compound, the 1,9-dimethyl MB (DMMB), which can have an enhanced interaction with cell membranes. Nevertheless, PDI mediated by DMMB to combat fungi remains little explored. In this study, we assessed the impact and underlying mechanisms of PDI using MB (MB-PDI) or DMMB (DMMB-PDI) combined with a red LED against *C. auris*. PDI was conducted on the CBS 10913 strain of *C. auris*, utilizing different concentrations of MB (0 – 100 μM) or DMMB (0 – 3 μM) at light doses of 10 or 30 J/cm². To evaluate the PDI efficacy, we measured colony-forming units and monitored reactive oxygen species (ROS) production. Additionally, we assessed lipid peroxidation (LPO) and mitochondrial membrane potential (ΔΨm) to gain insights into the differences between MB and DMMB. Our findings revealed that DMMB-PDI successfully eradicated *C. auris* yeasts at 3 μM concentration, irrespective of the light dose, whereas MB (100 μM) only exhibited cell eradication at the highest light dose. ROS formation was more pronounced for DMMB than MB at 10 J/cm^2. At 30 J/cm^2, MB and DMMB produced similar ROS levels. In sublethal conditions, DMMB-PDI induced significantly higher LPO, and ΔΨm levels compared to MB-PDI. Furthermore, DMMB-PDI effectively inhibited biofilm formation and disrupted mature biofilms, with no observed toxicity in fibroblast cells. In conclusion, our study demonstrates the potential of DMMB-PDI as a promising weapon to combat the global priority pathogen *C. auris*. The enhanced PDI efficacy and biofilm eradication capacity of DMMB make it a valuable candidate for further exploration in the fight against this hazardous pathogen. As the incidence of drug-resistant fungal infections continues to rise, the development of innovative and effective therapeutic strategies like DMMB-PDI is crucial in safeguarding public health worldwide.

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