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ORIGINAL ARTICLE/ARTICLE ORIGINAL

A diterpenoid taxodone from *Metasequoia glyptostroboides* with antimycotic potential against clinical isolates of *Candida* species

Une taxodone diterpenoïde de Metasequoia glyptostroboides *avec une activité antifongique potentielle contre des isolats cliniques de* Candida *sp.*

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KEYWORDS
Metasequoia glyptostroboides;
Antimycotic potential;
Taxodone;
Candida species;
Clinical isolates

Summary
Objective. — The increasing importance of clinical isolates of *Candida* species and emerging resistance of *Candida* species to current synthetic antifungal agents have stimulated the search for safer and more effective alternative drugs from natural sources. This study was directed towards exploring the antimycotic potential of a diterpenoid compound taxodone isolated from *Metasequoia glyptostroboides* against pathogenic isolates of *Candida* species.
Materials and methods. — Antimycotic efficacy of taxodone was evaluated by disc diffusion assay, determination of minimum inhibitory (MIC) and minimum fungicidal (MFC) concentrations, and cell viability assay. To confirm a partial antimycotic mode of action of taxodone, the efficacy of taxodone was determined by measuring the release of 260 nm absorbing materials from the selected *Candida* species as compared to control.
Results. — The taxodone at the concentration of 400 μg/disc displayed potential antimycotic effect against the tested clinical and pathogenic isolates of *Candida* species as diameters of zones of inhibitions, which were found in the range of 11 ± 0.0 to 12.6 ± 0.5 mm. The MIC and MFC values of taxodone against the tested clinical isolates were found in the range of 250 to 1000 and 500 to 2000 μg/mL, respectively. On the other hand, the MIC and MFC values of positive control (amphotericin B) against the tested *Candida* isolates were found in the range of 62.5 to

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250 and 500 to 2000 μg/mL. On the viable counts of the tested fungal isolates, the taxodone exerted significant antimycotic effect. Elaborative study of partial mode of action conducted onto the release of 260 nm materials (DNA and RNA) revealed potential detrimental effect of taxodone on the membrane integrity of the tested pathogens at MIC concentration.
Conclusion. — With respect to the antimycotic effect of taxodone against pathogenic and clinical isolates of *Candida* species, it might be confirmed that bioactive compound taxodone present in *M. glyptostroboides* holds therapeutic value of medicinal significance.

MOTS CLÉS
Metasequoia glyptostroboides ;
Potentiel antifongique ;
Taxodone ;
Candida sp. ;
Isolats cliniques

Résumé
Objectifs. — L'importance croissante des isolats cliniques de *Candida albicans* et l'émergence de résistance de *Candida* sp. aux antifongiques synthétiques actuels ont stimulé les recherches vers des produits alternatifs plus sûrs et plus efficaces issus de sources naturelles. Cette étude a exploré le potentiel actif d'un composé taxodone diterpénoïde isolé de *M. glyptostroboides*, contre des isolats pathogènes de *Candida* sp.
Matériel et méthodes. — L'effet antifongique de la taxodone a été évalué par la méthode de diffusion avec des disques, par la détermination de la concentration minimale inhibitrice (CMI) et fongicide (CMF) et par un test de viabilité. Une action antifongique partielle de la taxodone a été confirmée par la mesure à 260 nm du matériel relargué par les souches de *Candida* choisies en comparaison avec une souche témoin.
Résultats. — La taxodone à la concentration de 400 μg/disque a montré un effet antifongique contre les isolats testés, avec des diamètres d'inhibition de 11 ± 0 et 12,6 ± 0,5 mm. La CMI et la CMF de la taxodone étaient 250 à 1000 et de 500 à 2000 μg/mL, respectivement ; en outre, la CMI et la CMF de l'amphotéricine B, comme témoin, contre les mêmes isolats étaient de 62,5—250 et 500—2000 μg/mL. La taxodone montrait un effet antifongique significatif sur la viabilité des isolats testés. L'étude sur le mode d'action partiel basée sur le relargage de matériel (ADN et ARN) à 260 nm révélait un effet délétère de la taxodone sur l'intégrité membranaire des pathogènes testés à la CMI.
Conclusions. — Concernant l'effet antifongique de la taxodone contre des isolats cliniques et pathogènes de *Candida* sp., il semble confirmé que ce composé bioactif présent dans *M. glyptostroboides* possède une valeur thérapeutique significative sur le plan médical.

Introduction

Candida species are the most important factors for human fungal infections with immune deficiency states or other predisposing factors [15]. They have been shown to be the causative agents of many infections in an increasing range of anatomical sites and clinical settings [15]. In normal healthy individuals, the yeast *Candida* is classified as a commensal organism that can colonize both internal and external surfaces. Under these circumstances, an equilibrium between the host and the yeast microflora ensures a virulent, commensal status of this microorganism. The onset of candidosis in people infected with human immunodeficiency virus (HIV) is considered to be closely related to manifestation of AIDS and AIDS-related diseases. Although *Candida albicans* has been implicated in the early stages of AIDS, infections due to other *Candida* species are becoming more widespread in late-stage AIDS [9].

The increased local and systemic disease prevalence caused by *Candida* species has resulted in numerous new clinical syndromes. *Candida* species produce a wide spectrum of diseases, ranging from superficial mucocutaneous disease to lethal form of diseases, such as septicaemia, hepatosplenic candidiasis, *Candida* peritonitis, and systemic candidiasis [23]. Candidiasis caused by *Candida* species is one of the most common fungal infections especially by *C. albicans* and recurrent candidiasis causes severe complications in women referring to clinical diagnosis. The management of serious and life-threatening invasive candidiasis remains severely hampered by the lack of reliable antimycotic drugs that allow both fungemia and tissue invasion by *Candida* species.

Oral mycotic infections have been treated with polyene antifungals, such as amphotericin B or nystatin, and with azoles, such as clotrimazole or miconazole. The high relapse rate and reported toxic side effects of amphotericin B led to the use of azoles as the first line of treatment [7]. Because ketoconazole and itraconazole are not as readily absorbed, their use has been limited. Although fluconazole has become the agent of choice in antimycotic therapy, its widespread use has resulted in an increase in resistance of *Candida* to its antifungal efficacy [1]. Because of the rising incidence of failures in the treatment of mycoses in the case of severely immunosuppressed patients, there is a need for the development of new therapeutic agents that support the antifungal activity of antimycotics [24].

In order to overcome these problems, plant-based bioactive constituents could be served as potential biomedicinal tools for using in medicine industry to control serious fungal infection caused by *Candida* species. Plant-based bioactive