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ORIGINAL ARTICLE/ARTICLE ORIGINAL

Anticandidal synergistic activity of green tea catechins, antimycotics and copper sulphate as a mean of combinational drug therapy against candidiasis

Activité synergique Anticandidal de catéchines du thé vert, antimycosiques et sulfate de cuivre comme moyen de thérapie médicamenteuse combinational contre la candidose

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KEYWORDS

Green tea catechins;
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Summary The present investigation aims at evaluating synergistic herbal based composition of purified catechins with fluconazole, amphotericin B and copper sulphate against *Candida albicans* (MTCC 3017) and *Candida glabrata* (MTCC 3019). The catechins were isolated from green tea leaves of Assam, Himachal Pradesh and Uttarakhand regions of India. The synergistic activity of combinations against *Candida* species was assessed following microdilution checkerboard technique and time kill assay. The inhibitory action of most significant combination on treated *Candida* cells was assessed by scanning electron microscopy. Cytotoxicity of synergistic compositions was further analyzed by performing MTT assay on Vero cell lines. Purified catechins of Assam and Himachal Pradesh green tea showed synergistic activity with fluconazole and amphotericin B against *Candida* species. Time kill assay depicted synergistic activity at minimum inhibitory concentration and twice of minimum inhibitory concentration of purified catechins and antimycotics. Further, Copper sulphate increased anticandidal efficacy of synergistic

Abbreviations: EGCg, epigallocatechin gallate; GT, green tea; AT, Assam green tea; HP, Himachal Pradesh green tea; IP, PN, Uttarakhand green tea; CU, copper sulphate; Flu, Fluconazole; AmB, Amphotericin B; YPD Agar, Yeast Peptone Dextrose Agar; YPD broth, Yeast Peptone Dextrose broth; MIC, minimum inhibitory concentration

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MOTS CLÉS

Vert catéchines du thé ;
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combinations by 0.4% to 6.63%. SEM analysis revealed morphological distortions of treated *Candida* cells. Cytotoxicity analysis of synergistic composition depicted high percentage viability ($\geq 91.4\%$ to $\geq 100\%$) of Vero cell line, which suggests non-cytotoxic activity of proposed composition on healthy cells. It can be inferred that present evaluated synergistic composition can confer promising anticandidal efficacy and requires further investigation of safety and translational guidelines for effective and safer green tea based potent therapeutic drug.

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Résumé La présente enquête vise à évaluer synergique composition à base d'herbes de catéchines purifiées avec le fluconazole, l'amphotéricine B et de sulfate de cuivre contre *Candida albicans* (MTCC 3017) et *Candida glabrata* (MTCC 3019). Les catéchines ont été isolés à partir de feuilles de thé vert de l'Assam, Himachal Pradesh et Uttarakhand régions de l'Inde. L'activité synergique des différentes combinaisons contre les espèces de *Candida* a été évaluée suivant la technique de microdilution en damier et un essai de tuer le temps. L'action inhibitrice de la plus importante combinaison(s) sur les cellules de *Candida* traitées a été évaluée par microscopie électronique à balayage. Cytotoxicité des compositions synergiques a en outre été analysée en réalisant un test MTT sur des lignées cellulaires Vero. catéchines purifiées de thé vert Assam et de l'Himachal Pradesh ont montré une activité synergique avec le fluconazole et l'amphotéricine B contre les espèces de *Candida*. Temps de dosage tués représenté une activité synergique à une concentration minimale inhibitrice (CMI) et deux fois la concentration minimale inhibitrice (2MIC) des catéchines et des antimycotiques purifié. En outre, le sulfate de cuivre a augmenté l'efficacité anticandidal des combinaisons synergiques de 0,4 % à 6,63 %. Analyse par MEB a révélé des distorsions morphologiques des cellules de *Candida* traitées. Analyse de la cytotoxicité de la composition synergique représentée une viabilité élevée en pourcentage (% aux $\geq 91,4 \geq 100$ %) de la lignée cellulaire Vero qui suggère une activité non cytotoxique de la composition proposée sur les cellules saines. Dans l'on peut déduire que présente composition synergique évaluée peut conférer une efficacité prometteuse anticandidal et nécessite une enquête plus approfondie sur la base de directives de sécurité et de traduction pour le développement de médicaments thérapeutiques puissants à base de thé vert efficace et plus sûre.

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Introduction

Green tea (GT) is derived from leaves of *Camellia sinensis* and is in one of the purest and most infiltrated forms of tea. GT has greatly persuaded human health from generations and with frequent experimental evidences, people have recognized its considerable health benefits [1–6]. The multipotential effects of GT are credited to its rich presence of catechins, which confers GT with high antioxidant, antimicrobial activity against growth of resistant and opportunistic pathogens [7–13].

Green tea polyphenols (GTPs) includes flavonols which are attributed with rich catechins composition comprising mainly of (–)-epigallocatechin-3-gallate (EGCg), (–)-epigallocatechin (EGC), (–)-epicatechin (EC), (–)-epicatechin-3-gallate (ECG), (+)-gallocatechin, and (+)-catechin [14–16]. EGCg is the most significant catechin, which has been investigated as potent antimicrobial agent. Other than its antimicrobial potential, synergistic effect of EGCg with antimycotics has been established against pathogenic bacterial and fungal species [6,15,17].

The heightened predominance of local and systemic diseases caused by *Candida* species has resulted in numerous new clinical syndromes, which renders unsuccessful therapies in prevention of candidiasis [18]. *Candida* is one of the frequently encountered opportunistic fungal pathogen associated with diverse spectrum of pathogenicity contributing in

superficial candidiasis to life-threatening systemic candidiasis in immunodeficients, AIDS, intensive care patients and organ transplant recipients with mortality rate of 10%–49% [19–22]. Incompetent diagnostic methods and non-benefiting antimycotic therapies have alarmingly increased mortality rates of candidiasis [23,24].

Synergistic utilization of antibiotics and bioactive plant extracts is a novel perception and could be beneficial or deleterious in a sense that the combining herbal extracts and antibiotics together can outcomes with inhibition of microbial pathogens or it may happen that the combination is as effective as their individual therapeutic potential [25]. Studies have indicated that combined treatment of EGCg and antimycotics enhances inhibitory effect of amphotericin B or fluconazole and can confer efficient antimycotic potential against antimycotic-susceptible and resistant *Candida albicans* at substantially lower dose [1].

Heavy metals at relatively lower concentration also act as inhibitor of microbial growth. Copper as an essential enzyme cofactor drives significant biochemical processes and studies have reported its biocidal properties in preventing and controlling growth of a wide variety of microbes [26,27]. However, microbes have tendency to develop copper resistance in the presence of excess of copper in the environment [28]. Thus, keeping in view the potency and properties of copper, the present investigation aims at evaluating synergistic herbal based composition of purified catechins isolated

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