

TITLE: SYNERGIC COMBINATION BETWEEN HERBAL MEDICINE AND FLUCONAZOLE AGAINST *Cryptococcus gattii*

AUTHORS: ROCHA, C.H.L.; ROCHA, F.M.G.; HOLANDA, R.A.; SILVA, L.C.N.; MONTEIRO, C.A.; SANTOS, J. R. A.

INSTITUTION: UNIVERSIDADE CEUMA - UNICEUMA, SÃO LUÍS, MA (RUA JOSUÉ MONTELLO, Nº 1, RENASCENÇA II, SÃO LUÍS-MA, CEP 65.075-120)

ABSTRACT:

Herbal medicines as *Terminalia catappa* represent a promising alternative for treatment against microbial diseases once the augment of antimicrobial resistance of some strains have been described in relation to the use of conventional drugs. Furthermore, the combination between antimicrobial compounds from *Terminalia catappa* and conventional drugs could be used in an attempt to avoid the emergency of resistant strains coming from the monotherapy employed. In this context, we evaluated the antifungal activity of n-butanol fraction from *Terminalia catappa* leaves alone or combined with fluconazole against *Cryptococcus gattii*. All assays were performed using the *C. gattii* L27/01 and 547 strains from CEUMA University Culture Collection and the *C. gattii* ATCC 24065 as reference strain. Minimum Inhibitory Concentration (MIC) of n-butanol fraction from *Terminalia catappa* leaves and Fractional Inhibitory Concentration (FIC) with fluconazole were determined against *C. gattii* strains, as well as the time kill curves were also performed. Against all *C. gattii* strains used, n-butanol fraction showed 100% inhibitory activity (MIC₁₀₀) ranging from 0,18 to 3 mg/mL, whereas fluconazole concentration showed 100% (MIC₁₀₀) and 50% (MIC₅₀) inhibitory activities ranging from 8 to 16 µg/mL and 4 to 8 µg/mL, respectively. FIC results showed a synergism effect between n-butanol fraction and fluconazole (CIF < 0,5) against all *C. gattii* strains. The time kill curves corroborated FIC results displaying the dynamism of the action of these two substances either alone or in combination. Here, we demonstrate the potential of *Terminalia catappa* fraction as antifungal agent, albeit the mechanism of action, toxicity assays and *in vivo* studies are needed in order to better clarify it.

Keywords: Synergic combination, *Cryptococcus gattii*, inhibition, antifungal agents, herbal medicine.

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