TITLE: CROSS RESISTANCE BETWEEN AGROCHEMICALS AND CLINICAL ANTIFUNGALS IN PATHOGENIC YEASTS

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ABSTRACT:

Brazil is the world's largest consumer of agrochemicals, and Maranhão is the 10th consumer among Brazilian states. Fungicide agrochemicals have the function of inhibiting the growth of fungi that are pathogens of agriculture. However, human pathogenic fungi are also present in the environment associated with soil, plants and decomposing materials. The use of pesticides and their persistence in the environment favors the emergence and propagation of fungi resistant to the azoles due to the reduction in ergosterol levels of the fungal cell membrane. Studies suggest that the use of agrochemicals influences the clinical antifungal resistance. The objective of this study was to investigate the cross-resistance between agrochemicals and antifungal agents of clinical use against *Cryptococcus neoformans* and *Candida albicans*. The minimum inhibitory concentration (MIC) for epoxiconazole (EPZ), carbendazim (CBZ) fluconazole (FCZ), and amphotericin B (AMB) were determined by the microdilution method. Minimum Inhibitory Concentration (MIC) against clinical isolate of *Cryptococcus neoformans* and *Candida albicans* ATCC 90028 before and after contact with fungicides agricultural were determined. The highest MIC against *C. neoformans* and *C. albicans* was observed for carbendazim (64 μg/mL), while the values for amphotericin B (2 μg /mL), fluconazole MIC (0.5 μg/mL) and epoxiconazole (0.25 μg/mL) were lower. However, after contact with epoxiconazole or carbendazim, MIC values increased 4-fold for fluconazole (8 μg/mL) and 3-fold for amphotericin B (16 μg/mL) against *C. neoformans*, while the values remained the same for fluconazole against *C. albicans*. Interestingly, the susceptibility profile after contact with the agrochemicals was different between *C. albicans* and *C. neoformans*. These results confirm the possibility of cross-resistance between agricultural fungicides and the main antifungal agents of clinical use. In addition to the risk of exposure, the use of these pesticides may result in cross-resistance with azole of medical interest, which rekindles awareness of the indiscriminate use of pesticides and may be one of the hypotheses of primary resistance that has been observed during the treatment of cryptococcosis.

Keywords: *Cryptococcus*; *Candida;* pesticides; resistance.

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