Title: CARVACROL AND ANTITUBERCULOUS DRUGS COMBINATIONS IN *Mycobacterium tuberculosis*

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Abstract:

The high morbidity and mortality rates associated with tuberculosis (TB) are one of the aspects that characterizes the disease as an important public health problem worldwide. TB is a curable disease if the patients are properly treated. However, anti-TB first line, rifampicin (RIF), isoniazid (INH), ethambutol (EMB), streptomycin (STR), and pyrazinamide (PZA), which are routinely used against TB, have become therapeutically ineffective in some situations, due to the increased incidence of resistant bacillus. The emergence of multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), especially in cases of co-infection with HIV, are a major concern for the control of TB epidemia. Multidrug therapy is essential for the treatment of TB and is the basis for avoiding drug resistance and each new proposed anti-TB drug needs to be previously evaluated with regard to its interactions with other drugs to avoid antagonism. The carvacrol (CAR) is abundantly found in aromatic plants such as oregano and tomilho, has antioxidant activity, anti-microbial, anti-cancer among others. Knowing the anti- *Mycobacterium tuberculosis* activity in a previous study, the aim of the present study was to evaluate the effect of CAR combined with anti-TB drugs in *M. tuberculosis*. The combination of CAR with RIF or INH or ETB were tested in triplicate for *M. tuberculosis* $H_{37}Rv$ and two clinical isolates (one pan-susceptible and one MDR) using the Resazurin Drugs Combination Microtiter Assay (REDCA) method. To evaluate the synergistic effect for all drugs combination, the fractional inhibitory concentration index (FICI) for each combination was determined. The results were interpreted by the FICI as: synergism, 0.50; indifference, >0.50 - 4; and antagonism, >4. The CAR/RIF combination showed synergism in *M. tuberculosis* $H_{37}Rv$ and in the pan-susceptible isolate. For the MDR isolate studied no drug combination showed to have synergic effect. Although with the limitations for the use of a small number of isolates studied, no antagonism with the tree first-line anti-TB drugs was observed and the results in the present study corroborate with to the literature. The present study is the first insight about the importance to continue studies with CAR/anti-TB drugs combinations, which should be considered in the development of new therapeutic strategies to prevent the emergence of bacillus resistance during treatment of TB.

Key-words: Mycobacterium tuberculosis, Carvacrol, Drug interactions

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