SYNERGISM AMONG EFFLUX PUMP INHIBITORS AND ANTIMICROBIALS IN *Mycobacterium tuberculosis*

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Tuberculosis (TB) is an infectious bacterial disease caused mainly by *Mycobacterium tuberculosis* and currently is a health public problem in the world. TB is a curable disease if the patients are properly treated. However, several anti-TB first line drugs such as 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. Among different causes of bacterial resistance, the efflux pump systems have been recognized to have an important role in antibiotic resistance in mycobacteria. Some studies have reported that the activity of antibiotics can be significantly enhanced by co-administration with efflux pump inhibitors (EPIs). The aim of this study was to evaluate the effect of efflux pump inhibitors (EPIs), verapamil (VERA) and piperina (PIP) with first line anti-TB drugs and moxifloxacin (MO) combinations in *Mycobacterium tuberculosis*. The study was conducted in *M. tuberculosis* H_{37}Rv using the combinations of VERA and PIP with RIF, INH, ETB, SM and MO in *M. tuberculosis* H37Rv. The drugs interaction was assessed by Resazurin Drugs Combination Microtiter Assay (REDCA) method in duplicate. The fractional inhibitory concentration index (FICI) was calculated for each interaction and considered the values FICI ≤ 0.5 as synergistic, FICI > 0.5-4 as no interaction or additive effect and FICI > 4 as antagonism. The PIP/RIF and PIP/SM combinations showed synergistic effect in the bacillus. On the other side, no synergism was observed with VERA combinations. However, a decrease in the MIC value of RIF was observed with VERA/RIF combinations. No antagonism was observed. The result of this study is an insight about the importance to continue the studies with EPIs/anti-TB drugs combinations, which should be considered in the development of new therapeutic strategies to prevent the emergence of bacillus resistance during treatment.

Keywords: Tuberculosis, Synergism, REDCA.

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