

Title: INVESTIGATION OF *IN VITRO* ANTIMYCOBACTERIAL ACTIVITY OF NATURAL COMPOUNDS FROM BRAZILIAN ASTERACEAE PLANTS

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Resume:

Tuberculosis is a serious public health problem worldwide with one-third of the world's population estimated to be infected with *Mycobacterium tuberculosis*. Tuberculosis treatment requires the use of multiple drugs for at least 6 months. This lengthy drug therapy and adverse reactions to the drugs contribute to patient non-compliance, resulting in treatment failure and the emergence of *M. tuberculosis* drug resistant strains. There is an urgent need for new drugs to treat tuberculosis and natural products represent important sources for drug discovery. The aim of this study was to evaluate the in vitro antimycobacterial activity of crude plant extracts and isolated plant-derived compounds in reference strains and clinical isolates. Primary screening was conducted with 8 extracts from *Calea pinnatifida* and *Calea uniflora* and 18 purified compounds against *M. tuberculosis*, *M. avium* and *M. fortuitum* at concentrations ranging from 1.56 to 100 µg/mL. Five extracts and 10 specific compounds showed antimicrobial activity against *M. tuberculosis* with minimum inhibitory concentrations (MIC) ranging from 25 to 100 µg/mL for the extracts and 6.25 to 100 µg/mL for the compounds. Six sesquiterpene lactones were tested against clinical isolates of *M. tuberculosis* (drug-resistant and susceptible strains) and showed similar MIC compared to the reference strain. The compounds did not show synergism or antagonism in combination with the front-line tuberculosis-drug isoniazid. Compound selectivity index ranged from 1.77 to 11.88 in MRC5 lung cell line cytotoxicity tests. *In silico* modelling indicate that these compounds may work as nuclear receptor ligands or enzyme inhibitors. Further studies using transcriptional profiling and mutagenesis will be performed to evaluate compound mode of action.

Key words: Tuberculosis, new antitubercular drugs, sesquiterpene lactones.