TITLE: THIOSEMICARBAZIDE (-)-CAMPHENE DERIVATIVE RESCUES POLYMYXIN B ACTIVITY AGAINST CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE*

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ABSTRACT:

Enterobacteriaceae can be to become resistant to the latest generation antimicrobials, such as carbapenems. In this sense, polymyxin B (PMB) has been one of the available resources for treating carbapenem-resistant *Enterobacteriaceae* (CRE) infections. However, PMB-resistant isolates are emerging as PMB have been used in clinical practice. In order to contribute to the reduction of the toxicity and resistance, drug association has been used as a therapeutic alternative for patients with CRE infections. Camphene, a naturally occurring monoterpene found in high concentrations in the essential oil of leaves and flowers of various plant species, has been used to the synthesis of thiosemicarbazide. In addition, thiosemicarbazide (-)-camphene derivative (TSC) has antimicrobial activity reported in fungi and bacteria. In this sense, we aim to evaluate the action of TSC combined with PMB in CRE isolates. The PMB and TSC minimum inhibitory concentration (MIC) were determined by broth microdilution methods. The effect of TSC on the activity of PMB in CRE was determined by modulation factor (MF), where MF = MIC of PMB/MIC of PMB+ TSC combination. A fourfold or greater reduction in the MIC of PMB combined with TSC was considered significant. The range of PMB concentration, adjusted according the previously determined MIC, was combined with TSC at a fixed concentration of 50 µg/mL. The PMB and TSC MICs ranged from 0.25 to 512 µg/mL and 625 to 1250 µg/mL, respectively, for all CRE isolates tested. The TSC showed modulatory effect in PMB activity in all PMB-resistant isolates (MF ranged from 32 to 256). Thus, when TSC + PMB combination was employed, all PMB-resistant clinical isolates tested recovered susceptibility MICs. However, the same pattern of reduction in PMB MIC was not observed in PMB-susceptible clinical isolates. In conclusion, our results highlight the TSC modulatory effect in PMB activity rescuing the susceptibility of the CRE isolates for PMB.

Keywords: *Enterobacteriaceae*, polymyxin B, Drug Combinations, thiosemicarbazide

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