

**Title: MAPROTILINE INDUCES LOSS OF PLASMIDS CARRYING *bla*<sub>NDM-1</sub> IN ENTEROBACTERIACEAE**

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**Abstract:**

The production of Metallo- $\beta$ -lactamases such as NDM-1 by different bacterial species can efficiently inactivate carbapenems, the most potent antimicrobial class currently in clinical use for treatment of severe infections. The gastrointestinal tract is an important reservoir for dissemination of NDM-1-producing *Enterobacteriaceae*, mainly due to horizontal plasmid transfer. The evaluation of stability of plasmids carrying *bla*<sub>NDM</sub> genes is important for a better understand of the predominance of clones and for designing and discovering drugs that could reduce plasmid stability in clinical isolates belonging to *Enterobacteriaceae*. Maprotiline is currently used as an antidepressant medication and has shown a plasmid curing activity (plasmid loss) higher than 90% in *E. coli* K12. In this work we evaluated for the first time in the literature the ability of this compound to induce plasmid cure in different species hosting plasmids containing the *bla*<sub>NDM-1</sub> gene. A total of nine strains belonging to different species and subspecies were evaluated. The plasmid stability was determined by the plate counting method in LB agar, with and without previous treatment with maprotiline at subinhibitory concentrations (50 mg/L). The assay was conducted for 10 days representing approximately 100 generations. The data was analyzed using the statistical program R. When tested without previous exposure to maprotiline, *Providencia stuartii* showed a plasmid-curing rate of 45% and *Citobacter freundii* 26%. In *Escherichia coli* and *Klebsiella pneumoniae* the plasmid-curing rate was between 6-12%. *Enterobacter* spp. strains showed no plasmid-curing. When the strains were treated with maprotiline, the plasmid-curing increased significantly in *P. stuartii* (99.4%), *K. pneumoniae* (45%), *E. coli* (40-47%), *E. hormaechei* “subsp. steigerwaltii” (25%), while in *C. freundii* and *Enterobacter hormaechei* spp. “subsp. ohare” there was no significantly plasmid-curing effect. Maprotiline is a potential candidate for inducing plasmid loss in NDM-1-producing *Enterobacteriaceae* and potentially could contribute to reduce the dissemination of antimicrobial resistance if used in colonized patients.

**Key-words:** plasmid, *bla*<sub>NDM-1</sub>, *Enterobacteriaceae*, Maprotiline

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