代表性成果（四）

***Molecules* 共同通讯作者，为中科院 II 区 TOP 期刊，影响因子为 4.93。**

Shengnan Xie#, LiLi#, Baihe Zhan, Xue Shen, Xuming Deng, Wenxi Tan*, Tianqi Fang*, Pogostone Enhances the Antibacterial Activity of Colistin against MCR-1-Positive Bacteria by Inhibiting the Biological Function of MCR-1. *Molecules,* 2022, 04;27 (9).

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Article

Pogostone Enhances the Antibacterial Activity of Colistin against MCR-1-Positive Bacteria by Inhibiting the Biological Function of MCR-1

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Abstract: The emergence of the plasmid-mediated colistin resistance gene *mcr-1* has resulted in the loss of available treatments for certain severe infections. Here we identified a potential inhibitor of MCR-1 for the treatment of infections caused by MCR-1-positive drug-resistant bacteria, especially MCR-1-positive carbapenem-resistant *Enterobacteriaceae* (CRE). A checkerboard minimum inhibitory concentration (MIC) test, a killing curve test, a growth curve test, bacterial live/dead assays, scanning electron microscope (SEM) analysis, cytotoxicity tests, molecular dynamics simulation analysis, and animal studies were used to confirm the in vivo/in vitro synergistic effects of pogostone and colistin. The results showed that pogostone could restore the bactericidal activity of colistin against all tested MCR-1-positive bacterial strains or MCR-1 mutant–positive bacterial strains (FIC < 0.5). Pogostone does not inhibit the expression of MCR-1. Rather, it inhibits the binding of MCR-1 to substrates by binding to amino acids in the active region of MCR-1, thus inhibiting the biological activity of MCR-1 and its mutants (such as MCR-3). An in vivo mouse systemic infection model, pogostone in combination with colistin resulted in 80.0% (the survival rates after monotherapy with colistin or pogostone alone were 33.3% and 40.0%) survival at 72 h after infection of MCR-1-positve *Escherichia coli* (*E. coli*) ZJ487 (blaNDM-1-carrying), and pogostone in combination with colistin led to one or more order of magnitude decreases in the bacterial burdens in the liver, spleen and kidney compared with pogostone or colistin alone. Our results confirm that pogostone is a potential inhibitor of MCR-1 for use in combination with polymyxin for the treatment of severe infections caused by MCR-1-positive *Enterobacteriaceae*.

Keywords: MCR-1; pogostone; colistin; *Enterobacteriaceae*

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1. Introduction

The relentless rise in antibacterial resistance in extensively drug-resistant (XDR) and multidrug-resistant (MDR) Gram-negative pathogens poses a serious threat to human health. Especially in carbapenem-resistant *Enterobacteriaceae* (CRE), the treatment of drug-resistant bacterial infections is now challenging due to there being few therapeutic options [1–3]. Therefore, novel strategies are urgently required to address these serious clinical infections.

Colistin, a non-ribosomal cyclic lipopeptide antibiotic, is recognized as one of the last-choice antibiotics against multidrug-resistant Gram-negative bacteria [4]. At present, colistin resistance has risen along with the appearance and global spread of the mobile colistin resistance gene MCR, and additional MCR-like genes such as MCR-3 have been identified in *E. coli*, *Klebsiella pneumoniae* (*K. pneumoniae*), and/or *Salmonella typhimurium*