代表性成果（三）

业界公认顶刊 ***British Journal of Pharmacology*** 并列第一作者，为中科院 I 区 TOP 期刊（吉林大学 C 刊），影响因子为 **9.47**。

Wang Tingting[#], **Fang Tianqi[#],** Wang Xinyu, Zhang Can, Shen Xue, Deng Xuming*, Wang Jianfeng*, Amentoflavone attenuates Listeria monocytogenes pathogenicity through an LLO-dependent mechanism. ***British Journal of Pharmacology,*** 2022, 07;179 (14), 3839-3858.

Received: 22 July 2021 | Revised: 17 January 2022 | Accepted: 21 February 2022

DOI: 10.1111/bph.15827

RESEARCH ARTICLE

Amentoflavone attenuates *Listeria monocytogenes* pathogenicity through an LLO-dependent mechanism

Wang Tingting[1] | **Fang Tianqi**[1] | **Wang Xinyu**[1] | **Zhang Can**[1] | **Shen Xue**[2] | **Deng Xuming**[1] | **Wang Jianfeng**[1]

[1]State Key Laboratory for Zoonotic Diseases, Key Laboratory of Zoonosis Research, Ministry of Education, Institute of Zoonosis, College of Veterinary Medicine, Jilin University, Changchun, China

[2]Department of Food Science, College of Food Science and Engineering, Jilin University, Changchun, China

Correspondence
Wang Jianfeng and Deng Xuming, State Key Laboratory for Zoonotic Diseases, Key Laboratory of Zoonosis Research, Ministry of Education, Institute of Zoonosis, College of Veterinary Medicine, Jilin University, Changchun 130062, China.
Email: wjf927@jlu.edu.cn and Dengxm@jlu.edu.cn

Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 81861138046, NO.31902321, 31902321, 32172912; Fundamental Research Funds for the Central Universities, Grant/Award Number: 2020-JCXK-39

Background and Purpose: *L. monocytogenes* remain a leading cause of foodborne infection. Listeriolysin O (LLO), an indispensable virulence determinant involved in diverse pathogenic mechanisms of *L. monocytogenes* infection, represents a promising therapeutic target. In this study, we sought to identify an effective inhibitor of LLO pore formation and its mechanism of action in the treatment of *L. monocytogenes* infection.

Experimental Approach: Haemolysis assays were carried out to screen an effective LLO inhibitor. The interaction between candidate and LLO was investigated using surface plasmon resonance and molecular docking. The effect of candidate on LLO-mediated cytotoxicity, barrier disruption and immune response were investigated. Finally, the in vivo effect of candidate on mice challenged with *L. monocytogenes* was examined.

Key results: Amentoflavone, a natural flavone present in traditional Chinese herbs, effectively inhibited LLO pore formation by engaging the residues Lys93, Asp416, Tyr469 and Lys505 in LLO. Amentoflavone dose-dependently reduced *L. monocytogenes*-induced cell injury in an LLO-dependent manner. In the Caco-2 monolayer model, amentoflavone maintained the integrity of the epithelial barrier exposed to LLO. Amentoflavone inhibited the inflammatory response evoked by *L. monocytogenes* in an LLO-dependent manner, and inhibition was attributed to ability to block perforation-associated K^+ efflux and Ca^{2+} influx. In the mouse infection model, amentoflavone treatment significantly reduced bacterial burden and pathological lesions in target organs, with a significant increase in survival rate.

Conclusions and Implications: Amentoflavone reduced the pathogenicity of *L. monocytogenes* by specifically inhibiting LLO pore formation, and this may represent a potential treatment for *L. monocytogenes* infection.

KEYWORDS
amentoflavone, barrier function, immune response, *Listeria monocytogenes*, listeriolysin O (LLO) inhibitor

Abbreviations: AM, amentoflavone; CD, circular dichroism; CDC, cholesterol-dependent cytolysin; EM, electron microscope; LLO, listeriolysin O; MOI, multiplicity of infection; RMSF, root-mean-square fluctuation analysis; SPR, surface plasmon resonance; TEER, transepithelial electrical resistance.

Wang Tingting and Fang Tianqi contributed equally to this work.

