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Inhibitory Effect of Piceatannol on *Streptococcus suis* Infection Both *in vitro* and *in vivo*

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Suilysin (SLY) plays a critical role in *Streptococcus suis* infections making it an ideal target to the combat infection caused by this pathogen. In the present study, we found that piceatannol (PN), a natural compound, inhibits pore-formation by blocking the oligomerization of SLY without affecting the growth of *S. suis* and the expression of SLY. Furthermore, PN alleviated the J774 cell damage and the expression of the inflammatory cytokine tumor necrosis factor-α (TNF-α) and interleukin-1α (IL-1β) induced by *S. suis in vitro*. The computational biology and biochemistry results indicated that PN binds to the joint region of D2 and D4 in SLY, and Asn57, Pro58, Pro59, Glu76, Ile379, Glu380, and Glu418 were critical residues involved in the binding. The binding effect between PN and SLY hindered the SLY monomers from forming the oligomers, thereby weakening the hemolytic activity of SLY. This mechanism was also verified by hemolysis analysis and analysis of *KA* formation after site-specific mutagenesis. Furthermore, PN protected mice from *S. suis* infections by reducing bacterial colony formation and the inflammatory response in target organs *in vivo*. These results indicate that PN is a feasible drug candidate to combat *S. suis* infections.

Keywords: *Streptococcus suis*, piceatannol, suilysin, virulence, molecular modeling

INTRODUCTION

Streptococcus suis is a common Gram-positive bacterium that can cause a variety of infectious diseases in humans and pigs, including meningitis, arthritis, septicaemia, and pneumonia (Ajaree et al., 2018; Agoston et al., 2020). *Streptococcus suis* infection causes huge economic losses to the pig industry every year and seriously affects the health and development of the pig industry (Haas and Grenier, 2018). In addition, swine are important food-producing animals; *S. suis* induces human infection through infected pigs or their products. *Streptococcus suis* infection in humans is distributed globally and poses a serious threat to public health (Huong et al., 2014; Agoston et al., 2020; Olearo et al., 2020). With the development of bacterial resistance, great challenges in fighting with infections induced by *S. suis* have been encountered by humans (Seitz et al., 2016; Ma et al., 2018; Che et al., 2019). Therefore, the development of new drugs against this pathogen is of great significance for its prevention and control.