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Abstract

Resveratrol, A Novel Inhibitor of the NorA Efflux Pump and Resistance Modulator in *Staphylococcus aureus* †

Madalena Santos *, Raquel Santos and Susana Ferreira

CICS-UBI—Health Sciences Research Centre, University of Beira Interior, Avenida Infante D. Henrique, 6200-506 Covilhã, Portugal; raquel.neves.santos@ubi.pt (R.S.); susana.ferreira@fcsaude.ubi.pt (S.F.)

* Correspondence: madalena.santos@ubi.pt

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Abstract: Among the bacterial resistance mechanisms, active efflux pumps play a role in the extrusion of different molecules, and, thus, contribute to antimicrobial resistance. *Staphylococcus aureus* is a Gram-positive bacterium that can present resistance to various antibiotics, for which NorA, a predominant efflux pump of these strains, is known to promote resistant to fluoroquinolones. Thus, the inhibition of this efflux pump may modulate resistance in *S. aureus*, namely, to fluoroquinolones. Therefore, this study aimed to investigate the ability of a natural compound, resveratrol, to modulate fluoroquinolone resistance in *S. aureus*. The antimicrobial activity of resveratrol, ethidium bromide (EtBr) and norfloxacin was determined through the minimum inhibitory concentration (MIC). Then, the modulatory effect of resveratrol was evaluated by the determination of the MIC of the antibiotic or EtBr in the presence and absence of resveratrol at a sub-MIC level. The results showed that the MIC of norfloxacin against a wildtype *S. aureus* strain decreased by 2-fold, and for a NorA-overexpressing (norA++) strain decreased by 16-fold when in the presence of resveratrol. A similar behavior was observed for EtBr. Furthermore, an EtBr accumulation assay was also performed, showing that, in the presence of resveratrol, the norA++ strain had an augmented fluorescence as a consequence of the accumulation of EtBr. Altogether, the results suggested that resveratrol may act by inhibiting NorA. The postantibiotic effect (PAE) of norfloxacin alone and in combination with resveratrol was also determined, showing that the most extended PAE was observed with norfloxacin at 32 mg/L when tested in combination with resveratrol. Furthermore, there was a decrease in the mutation prevention concentration of norfloxacin when combined with resveratrol. Our findings demonstrated that resveratrol could modulate norfloxacin resistance by the inhibition of NorA, increasing the effectiveness of this antibiotic against *S. aureus*.

Keywords: efflux inhibition; NorA; resistance; resveratrol; *Staphylococcus aureus*

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