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Abstract

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

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Abstract: Among the bacterial resistance mechanisms, the active efflux pumps play a role in the extrusion of different molecules, and thus contribute for 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 fluoroquinolones resistance in *S. aureus*. The antimicrobial activity of resveratrol, ethidium bromide (EtBr) and norfloxacin were 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 presence and absence of resveratrol at a sub-MIC level. The results showed that the MIC of norfloxacin against in a wildtype *S. aureus* strain decreased by 2-fold and for a NorA overexpressing (norA++) strain decreased by 16-fold, when in presence of resveratrol. A similar behavior was observed for EtBr. Furthermore, EtBr accumulation assay was also performed, showing that in the presence of resveratrol, the norA++ strain had an augmented fluorescence, consequence of the accumulation of EtBr. Altogether, the results suggest that resveratrol may act by inhibiting NorA. The post-antibiotic 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 mutation prevention concentration of norfloxacin when combined with resveratrol. Our findings demonstrated that resveratrol could modulate the norfloxacin-resistance, by inhibition of NorA, increasing the effectiveness of this antibiotic against *S. aureus*.

Keywords: Covilhã; NorA; resistance; resveratrol; *Staphylococcus aureus*

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