Plant-derived stilbenoids as antimicrobial agents: interaction of resveratrol-derived monomers and dimers with model cell membranes

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Food contamination with pathogenic microorganisms, such as *Listeria monocytogenes*, *Salmonella enterica*, *Staphylococcus aureus*, and *Bacillus cereus*, is a common health concern. Unfortunately, the overuse and the misuse of antimicrobial agents in humans and animals have been leading to resistance mechanisms, which currently represent a recognized public health problem worldwide [1].

In this frame, natural products have always been a source of inspiration for new drugs and may represent a turning point in alleviating the antibiotic crisis. Stilbenoids are both woody constitutive metabolites and phytoalexins, which are substances produced by plants as means of protection against microbial infections and stress factors. Resveratrol and resveratrol-derived monomers and oligomers (stilbenoids), which can be extracted from several botanical sources such as grapes, cranberries, etc., have been shown to exert various biological activities [2,3].

Literature reports the evaluation of the antimicrobial activity of a collection of resveratrol-derived monomers and dimers against a panel of several foodborne pathogens, showing a variegated pattern of efficacies in terms of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) depending on both the chemical structure (shape and substitution pattern) and the nature of the microorganisms (gram-positive vs gram-negative). In some cases, morphological modifications on the cell membranes and leakage of intracellular content has been shown, suggesting that the cell membrane might be the principal biological target of such compounds [4].

In this scenario, starting from thermodynamic information about cell membranes recently reported by some authors [5,6], this study aimed at the investigation of the direct interaction of selected polyphenolic compounds with a model cell membrane in order to gain further insights on the possible molecular mechanisms lying under of the antimicrobial activity. The panel of tested compounds consisted in three specific monomer/dimer/dehydro-dimer sequences, namely 1) resveratrol / (±)-*trans*-δ-viniferin / dehydro-δ-viniferin, 2) pterostilbene / (±)-pterostilbene-*trans*-dihydrodimer / pterostilbene-dehydro-dimer, 3) resveratrol / (±)-*trans*-ε-viniferin / viniferifuran, hence including those compounds that have shown the highest and the lowest antimicrobial activities. The analyses were carried out through an integrated approach combining micro-DSC and mono and bidimensional NMR spectroscopy. DSC experiments were performed on Small Unilamellar Vesicles (SUVs) constituted by 2:3 DPPC:DSPC with incorporated polyphenols at physiological pH (pH 7.4) and results were well supported by complementary NMR data.

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