Grapevine stilbenoids as antimicrobial agents: thermodynamic determinants dictating stilbenoid-membrane interaction

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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 misuse of antimicrobial agents in humans and animals have been leading to resistance mechanisms, which currently represent a public health problem worldwide[1]. In this frame, considerable effort has been made to find naturally occurring compounds as effective and safe alternatives to the current antibiotics. In particular, resveratrol and the derived monomers and oligomers (stilbenoids) represent an attractive class of plant polyphenols studied in the last decades because of their various bioactivities[2,3]. Stilbenoids are both woody constitutive metabolites and phytoalexins, which are substances produced by plants as means of protection against microbial infections and stress factors, and can be extracted from several botanical sources. Recently, the antimicrobial activity of a collection of resveratrol-derived monomers and dimers has been evaluated against a panel of foodborne pathogens, and TEM analysis revealed severe morphological modifications on the cell membrane as well as leakage of intracellular content, suggesting that the membrane might be the principal biological target of such compounds[4].
In this scenario, basing on 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 role played by the cell membrane in the stilbenoid antimicrobial activity at a molecular level. 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, which include 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 were supported by complementary NMR data.

References

[1] Hammerum, A. M., Heuer, O. E. Human health hazards from antimicrobial-resistant *Escherichia coli* of animal origin. *Clin. Infec. Dis.*, 2009, 48, 916–921.

[2] Pezzuto, J. M. The Phenomenon of Resveratrol: Redefining the Virtues of Promiscuity. *Ann. NY Acad. Sci.*, 2011, 1215, 123–130.

[3] Akinwumi, B. C., Bordun, K. A. M., Anderson, H. D. Biological activities of stilbenoids. *Int. J. Mol. Sci.*, 2018, 19, 792.

[4] Mattio, L.M., Dallavalle, S., Musso, L., *et al*. Antimicrobial activity of resveratrol-derived monomers and dimers against foodborne pathogens. *Sci. Rep.*, 2019, 9, 19525.

[5] Saitta, F., Signorelli, M., Fessas, D. Dissecting the Effects of Free Fatty Acids on the Thermodynamic Stability of Complex Model Membranes Mimicking Insulin Secretory Granules. *Colloids Surf. B Biointerfaces*, 2019, 176, 167–175.

[6] Saitta, F., Signorelli, M., Fessas, D. Hierarchy of Interactions Dictating the Thermodynamics of Real Cell Membranes: Following the Insulin Secretory Granules Paradigm up to Fifteen-Components Vesicles. *Colloids Surf. B Biointerfaces*, 2020, 186, 110715.