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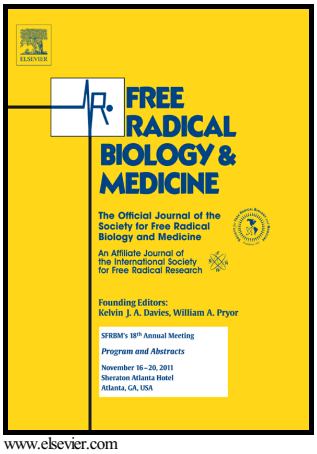

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PII: S0891-5849(17)31234-0
DOI: https://doi.org/10.1016/j.freeradbiomed.2017.12.002
Reference: FRB13537

To appear in: *Free Radical Biology and Medicine*

Received date: 24 October 2017
Revised date: 17 November 2017
Accepted date: 2 December 2017

Cite this article as: Hugo A.L. Filipe, Carla Sousa, Joaquim T. Marquês, Diogo Vila-Viçosa, António de Granada Flor, Ana S. Viana, M. Soledade C.S. Santos, Miguel Machuqueiro and Rodrigo F.M. de Almeida, Differential targeting of membrane lipid domains by caffeic acid and its ester derivatives, *Free Radical Biology and Medicine,* https://doi.org/10.1016/j.freeradbiomed.2017.12.002

Differential targeting of membrane lipid domains by caffeic acid and its ester derivatives

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Abstract

Phenolic acids have been associated to a wide range of important health benefits underlain by a common molecular mechanism of action. Considering that significant membrane permeation is prevented by their hydrophilic character, we hypothesize that their main effects result from the interplay with cell membrane surface. This hypothesis was tested using the paradigmatic caffeic acid (CA) and two of its ester derivatives, rosmarinic (RA) and chlorogenic (CGA) acids, for which we predict, based on molecular dynamics simulations, a shallow location in phospholipid bilayers dependent on the protonation-state. Using complementary experimental approaches, an interaction with the membrane was definitely revealed for the three compounds, with RA exhibiting the highest lipid bilayer partition, and the redox signals of membrane-bound RA and CA being clearly detected. Cholesterol decreased the compounds bilayer partition, but not their ability to lower membrane dipole potential. In more complex membrane models containing also sphingomyelin, with liquid disordered (l_d)/ liquid ordered (l_o) phases coexistence, mimicking domains in the external leaflet of human plasma membrane, all compounds were able to affect nanodomains lateral organization. RA, and to a lesser extent CGA, decreased the size of l_o domains. The most significant effect of CA was the possible formation of a rigid gel-like phase, enriched in sphingomyelin. In addition, all phenolic acids decreased the order of l_o domains. In sum, phenolic acid effects on the membrane are enhanced in cholesterol-rich l_o phases, which predominate in the outer leaflet of human cell membranes and are involved in many key cellular processes.

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