

MODULATION OF OXIDATIVE AND INFLAMMATORY PATHWAYS BY NATURE-INSPIRED NEW HYBRIDS: RELEVANCE FOR NRF2 TRANSCRIPTION FACTOR INVOLVEMENT.

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Oxidative stress and inflammation are common features of different disorders and the identification of new drugs acting on these pathways is an open field of research because of their potential application in different pathologies. Natural products offer great chemical diversity and have already proven to be a rich source of therapeutics. Polyphenols are widely diffused in nature and have been shown to modulate several pathways, including oxidative injuries. Diallyl sulfides are garlic-derived organosulfur compounds able to counteract oxidative stress through antioxidant phase II enzymes expression. In our previous paper, we combined these molecular fragments in chemical entities to produce hybrids with anti-oxidant and amyloid β (A β) anti-aggregant activity (Simoni et al. 2016) which have been the basis for the synthesis of different new derivatives.

To determine the potential interest of nature-inspired molecules as antioxidants, we investigated their protective effects against H₂O₂-induced oxidative damage. The scavenging effect on reactive oxygen species (ROS) was evaluated by using the fluorescent probe dichlorofluorescein diacetate (DCFH-DA) as a specific marker for the quantitative intracellular ROS formation. Furthermore, the expression of proteins involved in the anti-oxidant phase II response has been investigated by RT-PCR and western blot. In particular, we focused our attention on the Nrf2 transcription factor. Increasing evidence has revealed its involvement not only in regulation of the antioxidant phase II response, but also in suppressing inflammation through redox control and negative modulation of pro-inflammatory cytokine genes. Anti-inflammatory activity of nature-inspired compounds has been evaluated with ELISA commercial kits by analysis of the profile of IL-8, TNF- α and IL-1 β release. Our results confirmed the cross-talk between the Nrf2 pathway and the inflammation response. Moreover, one of our hybrids that does not allow Nrf2 nuclear translocation and activation, can modulate pro-inflammatory cytokine release, suggesting that these compounds can act directly also on one or more other pathways triggering Nrf2-independent anti-inflammatory response.

Bibliography: Simoni E, Serafini MM, Bartolini M, Caporaso R, Pinto A, Necchi D, Fiori J, Andrisano V, Minarini A, Lanni C, Rosini M. Nature-Inspired Multifunctional Ligands: Focusing on Amyloid-Based Molecular Mechanisms of Alzheimer's Disease. *ChemMedChem*. 2016 Jun 20;11(12):1309-17.