LONG-LASTING ANTI-INFLAMMATORY EFFECTS OF AMMONIUM GLYCYRRHIZINATE: AN INTEGRATED STUDY OF PHARMACOLOGY AND COMPUTATIONAL ANALYSIS

Federica Raucci[1], Paola Minosi[2], Amalia Di Giannuario[2], Maria Giovanna Chini[3], Simona De Vita[3], Giuseppe Bifulco[3], Francesco Maione[1], Stefano Pieretti[2], Nicola Mascolo[1]

[1]Department of Pharmacy, School of Medicine and Surgery, University of Naples Federico II, Naples - Italy, [2]National Centre for Drug Research and Evaluation, Istituto Superiore di Sanità, Rome - Italy, [3]Department of Pharmacy, University of Salerno, Fisciano (SA) - Italy

Introduction: Ammonium glycyrrhizinate (GA), an active ingredient of liquorice, is known to have various immune-modulating and inflammatory response-modifier activities. Recent studies have shown that liquorice extract can alleviate dermatitis, eczema, and psoriasis, with an efficacy comparable to that of corticosteroids. Moreover, it has been reported that GA is able to reduce the inflammatory events such as spinal cord injury, edema, tissue damage, apoptosis, iNOS expression, and NFκB activation. However, the mechanism underlying the *in vivo* anti-inflammatory activity of GA is not fully understood. Accordingly, the aim of the present investigation was to evaluate the potential long-lasting anti-inflammatory effects of GA by an integrated study of pharmacology and computational analysis.

Materials and methods: We evaluated the effects of GA in a mouse model of zymosan-induced peritonitis at both 4and 24h. The number of inflammatory infiltrates and the levels of pro-inflammatory cyto-chemokines were evaluated by the aim of quali-quantitative ElisaSpot assay. Finally, by docking studies, the modulation of key pro-inflammatory enzymes and pathways involved in the zymosan-related inflammation was also investigated.

Results: A single intraperitoneal (i,p.) injection of AG was able to produce anti-inflammatory effects followed to zymosan-induced peritonitis, decreasing the number of inflammatory infiltrates and reducing the levels of Interleukin (IL) -1β, -6, -10, Interferon Gamma-Induced Protein 10 (IP-10), Keratinocyte Chemoattractant (KC), Monocyte Chemotactic Protein 5(MCP-5), Macrophage Inflammatory Proteins (MIP) 1α, 1β and 2and Tumor Necrosis Factor (TNF)-α in the inflammatory fluids. Molecular docking studies also revealed that AG displays high affinity for Microsomal Prostaglandin E Synthase (mPGES) enzymes and it seems to be better located in the binding pocket of COX-2compared to COX-1enzyme.

Discussion and conclusion: These results demonstrated, for the first time, that AG after a single administration induced anti-inflammatory effects until 24h thanks to its ability to reduce the main pro-inflammatory pathways and mediators and further suggest that this natural active compound might be used for clinical treatment of pain condition and/or inflammatory related-diseases.