

Flavonoids and flavonoid-rich natural extracts inhibit cytokine release in cystic fibrosis bronchial epithelial cells by regulating NF- κ B pathway

Stefania Lucia Nori¹, Rita Patrizia Aquino², Vanessa Nicolin³, Antonietta Santoro²

¹ Faculty of Medicine and Pharmacy, Department of Medicine and Surgery, University of Salerno, Fisciano, Salerno, Italy - ² Faculty of Medicine and Pharmacy, Department of Pharmacy, University of Salerno, Fisciano, Salerno, Italy - ³ Clinical Department of Medical, Surgical and Health Science, University of Trieste, Trieste, Italy

Cystic fibrosis (CF) is a genetic life-shortening condition in Caucasians. Despite being a multi-organ disease, CF is classically diagnosed by symptoms of acute/chronic respiratory disease, with persistent pulmonary infections (Amaral, 2015). CF is caused by mutations in the gene encoding cystic fibrosis transmembrane conductance regulator (CFTR) protein. Inheritance of mutant CFTR alleles results in surface liquid depletion and defective mucociliary clearance leading to pulmonary failure. Defects in CFTR perturb the regulation of many intracellular signaling pathways including the NF- κ B pathway causing excessive production of pro-inflammatory mediators. Current CF therapies are directed to delay CF lung damage by restoring CFTR function and controlling abnormal inflammation. However, only few anti-inflammatory drugs are effective for CF treatments (mainly oral corticosteroids and ibuprofen), these drugs have limited beneficial effects in presence of considerable side effects. Flavonoids have been reported as promising anti-inflammatory drugs and some of them seem to act as CFTR direct activators (Amaral, 2015). From this respect, herbal remedies or plant bio-active molecules may be of great interest. To this aim, we tested the anti-inflammatory activity of apolar extracts from the roots of three *Peonia* species (*Paeoniaceae* family), namely *P. rockii*, *P. ostii* and *P. lactiflora*, on CFTR $\Delta F508/\Delta F508$ CuFi1 cells and normal counterpart. The effects of the extracts on intrinsic as well as TNF α -induced inflammation were evaluated by determining IL-8, IL-6 and RANTES production. Furthermore, to study the direct effect of the extracts on NF- κ B activation, Human Embryonic Kidney cells were used in transient transfection of NF- κ B reporter plasmid and NF- κ B activity and cytokine productions were also evaluated. Results showed a significant anti-inflammatory activity of all three *Peonia* extracts with the *P. lactiflora* being the most effective. Furthermore, we also tested the anti-inflammatory potential of the pure flavonoid naringin in the same model systems. We found that naringin was able to reduce cytokine release through inhibiting the key enzymes of the NF- κ B and MAPK/ERK pathways. Interestingly, preliminary results on spray dried pharmaceutical formulations of this molecule, show that naringin co-sprayed with leucine improves pharmacological activity of the flavonoid neat raw drug.

References

- [1] Amaral MD. (2015) Novel personalized therapies for cystic fibrosis: treating the basic defect in all patients. *J Intern Med.* 2015 277:155-66.

Keywords

Cystic Fibrosis airway epithelial cells; flavonoids; inflammation; nuclear transcription factor- κ B.