In vivo formed metabolites of polyphenols and their anti-inflammatory efficacy at intestinal level

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Introduction: Metabolites of polyphenols recently vested interest because of their actual bioavailability *in vivo*. In fact, they reach tissue concentrations that are likely responsible for the beneficial effects attributed to ingested polyphenols. The aim of our study was to evaluate the mechanisms of action of different classes of phase I/II metabolites of polyphenols coming from different plant foods against intestinal inflammation and epithelial barrier damage. Metabolites were tested in intestinal cell cultures to assess their efficacy against LPS-induced altered membrane permeability related to disruption and/or relocation of tight junction (TJ) proteins, as well as to the induction of iNOS expression associated to MAPKs and NF-κB pathways.

Material and methods: Human colon adenocarcinoma cells (Caco-2), differentiated as normal enterocytes, were treated with LPS (1 μg/mL) following pretreatment with the metabolites at concentration of 1-2.5 μM, which can be easily achieved *in vivo*. Caco-2 monolayers permeability was monitored with time, measuring the transepithelial electrical resistance (TEER). The modulation of MAPKs JNK, p38 and ERK1/2, and TJ zonulin (ZO-1) and occludin modification, were assessed by western blotting and immunofluorescence assays. Moreover, intestinal nitric oxide release consequently to iNOS expression, and modulation of Akt/IκBα/NF-κB pathway were also tested.

Results: Pretreatment with the tested metabolites decreased permeability and preserved TJ integrity. Moreover, LPS-induced MAPKs phosphorylation was significantly reduced. It was also observed that metabolites inhibited iNOS expression and counteracted IκBα degradation, through a modulatory action involving MAPKs and Akt pathways.

Conclusion: The outcome of this work indicates that metabolites are able to counteract LPS-induced alteration of epithelial permeability mainly through the modulation of MAPKs dependent intracellular signaling, thus they may significantly contribute to preserve the integrity of intestinal mucosa against inflammation related disorders.

Keywords: polyphenols; metabolites; inflammation; MAPK, intestinal permeability; metabolism