Prenylated polyphenols from Clusiaceae and Calophyllaceae with immunomodulatory activity on endothelial cells

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Résumé en anglais

Endothelial cells (ECs) are key players in inflammation and immune responses involved in numerous pathologies. Although attempts were experimentally undertaken to prevent and control EC activation, drug leads and probes still remain necessary. Natural products (NPs) from Clusiaceous and Calophyllaceous plants were previously reported as potential candidates to prevent endothelial dysfunction. The present study aimed to identify more precisely the molecular scaffolds that could limit EC activation. Here, 13 polyphenols belonging to 5 different chemical types of secondary metabolites (i.e., mammea coumarins, a biflavonoid, a pyranochromanone acid, a polyprenylated polycyclic acylphloroglucinol (PPAP) and two xanthones) were tested on resting and cytokine-activated EC cultures. Quantitative and qualitative changes in the expression of both adhesion molecules (VCAM-1, ICAM-1, E-selectin) and major histocompatibility complex (MHC) molecules have been used to measure their pharmaceutical potential. As a result, we identified 3 mammea coumarins that efficiently reduce (up to >90% at 10 μM) both basal and cytokine-regulated levels of MHC class I, class II, MICA and HLA-E on EC surface. They also prevented VCAM-1 induction upon inflammation. From a structural point of view, our results associate the loss of the free prenyl group substituting mammea coumarins with a reduced cellular cytotoxicity but also an abrogation of their anti-inflammatory potential and a reduction of their immunosuppressive effects. A PPAP, guttiferone J, also triggers a strong immunomodulation but restricted to HLA-E and MHC class II molecules. In conclusion, mammea coumarins with a free prenyl group and the PPAP guttiferone J emerge as NPs able to drastically decrease both VCAM-1 and a set of MHC molecules and to potentially reduce the immunogenicity of the endothelium.

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