Design, Synthesis, Pharmacological Evaluation and Vascular Effects of Delphinidin Analogues

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Résumé en anglais	BACKGROUND: Among polyphenolic compounds suggested to prevent cardiovascular diseases (CVDs) and to explain the "French paradox", the anthocyanidin delphinidin (Dp) has been reported to support at least partly the vascular beneficial effects of dietary polyphenolic compounds including those from fruits and related products as red wine. It has also been highlighted that Dp interacts directly with the active site of estrogen receptor α (ERα), leading to activation of endothelial NO synthase (eNOS) pathway thus contributing to the prevention of endothelial dysfunction in mice aorta. However, anthocyanidins have very low bioavailability and despite a well described in vitro efficacy, the very high hydrophilicity and physicochemical instability of Dp might explain the lack of in vivo reported effects. OBJECTIVE: The aim of this study was to identify new Dp analogues with increased lipophilicity and vasorelaxation potential by a chemical modulation of its structure and to characterize the signaling pathway notably in relation with ERα signaling and nitric oxide (NO) production. METHOD: OCH3-substituted delphinidin analogues were obtained through the coupling of the corresponding acetophenones with substituted benzaldehydes. Prediction of resorption of the flavylium derivatives was performed with the calculated logP and induction of vasorelaxation was performed by myography on WT and ERαKO mice thoracic aorta rings and compared to Dp. NO production was evaluated in vitro on human primary endothelial cells. RESULTS: Eight Dp analogues were synthesized including four new flavylium derivatives. Two compounds (9 and 11) showed a strong increase of vasorelaxation potential and a theoretically increased bioavailability compared to Dp. Interestingly, 9 and 11 induced increased O2 - or NO endothelial production respectively and revealed a novel NO-dependent ERα-independent relaxation compared to Dp. We suggested that this mechanism may be at least in part supported by the inhibition of vascular cyclic nucleotide phosphodiesterase (PDEs). CONCLUSION: The current study demonstrated that pharmacomodulation of the Dp backbone by replacement of OH groups by OCH3 groups of the A and B rings led to the identification and characterization of two compounds (9 and 11) with enhanced physio-chemical properties that could be associated to higher permeability capability and pharmacological activity for the prevention of CVDs compared to Dp.
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