Structure-activity relationship of coumarin derivatives on xanthine oxidase-inhibiting and free radical-scavenging activities

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摘要

Abstract

We employed 1,1-diphenyl-2-picrylhydrazyl hydrate (DPPH)- and 5,5-dimethyl-1-pyrroline-N-oxide (DMPO)-electron spin resonance (ESR) to study the effects of suppression of reactive oxygen species (ROS) by eight selected coumarin derivatives under oxidative conditions. Esculetin was the most potent radical scavenger among the eight tested compounds. Our results suggest that the number of hydroxyl groups on the ring structure of coumarins is correlated with the effects of ROS suppression. We also investigated the effect of the derivatives on the inhibition of xanthine oxidase (XO) activity, and the structure-activity relationships (SARs) of these derivatives against XO activity were further examined using computer-aided molecular modeling. All determined derivatives competitively inhibited XO. The results of the structure-based molecular modeling exhibited interactions between coumarins and the molybdopterin region of XO. The carbonyl pointed toward the Arg880, and the ester O atom formed hydrogen bonds with Thr1010. Esculetin, which bears two hydroxyl moieties on its benzene rings, had the highest affinity toward the binding site of XO, and this was mainly due to the interaction of 6-hydroxyl with the E802 residue of XO. The hypoxanthine/XO reaction in the DMPO-ESR technique was used to assess the combined effect on enzyme inhibition and ROS suppression by these coumarins, and the results showed that esculetin was the most potent agent among the tested compounds. We further evaluated the effects of the test compounds on living cells, and esculetin was still the most potent agent at protecting cells against ROS-mediated Abeta-damage among the tested coumarins.