Structure-activity relationship of C6-C3 phenylpropanoids on xanthine oxidase-inhibiting and free radical-scavenging activities

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摘要

Abstract

We employed the techniques of DNA relaxation, DPPH (1,1-diphenyl-2-picrylhydrazyl hydrate), and DMPO (5,5-dimethyl-1-pyrroline-N-oxide)-electron spin resonance (ESR), to study the effects of reactive oxygen species (ROS) suppression by 11 selected C6-C3 phenylpropanoid derivatives under oxidative conditions. We also investigated the effects 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. Caffeic acid was the most potent radical scavenger among the 11 test compounds. Our results suggest that the chemical structure and number of hydroxyl groups on the benzene ring of phenylpropanoids are correlated with the effects of ROS suppression. All test derivatives were competitive inhibitors of XO. The results of the structure-based molecular modeling exhibited interactions between phenylpropanoid derivatives and the molybdopterin region ofXO. The para-hydroxyl of phenylpropanoid derivatives was pointed toward the guanidinium group of Arg 880. The phenylpropanoid derivatives containing the meta-or ortho-hydroxyl formed hydrogen bonds with Thr 1010. In addition, meta-hydroxyl formed hydrogen bonds with the peptide bond between the residues of Thr1010 and Phe1009. CAPE, the phenylenethyl ester of phenylpropanoids, had the highest affinity toward the binding site of XO, and we speculated that this was due to hydrophobic interactions of the phenylethyl ester with several hydrophobic residues surrounding the active site. The hypoxanthine/XO reaction in the DMPO-ESR technique was used to correlate the effects of these phenylpropanoid derivatives on enzyme inhibition and ROS suppression, and the results showed that caffeic acid and CAPE were the two most potent agents among the tested

compounds. We further assessed the effects of the test compounds on living cells, and CAPE was the most potent agent for protecting cells against ROS-mediated damage among the tested phenylpropanoids.