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Caffeic acid-derived biopolymer, synthesis of its monomer and methylated derivative and their comparative anticancer efficacy

Vakhtang Barbakadze
Tbilisi State Medical University, Georgia

According to data of 13C, 1H-NMR, 2D heteronuclear 1H/13C HSQC, 1D NOE and 2D DOSY experiments, the main chemical constit¬uent of high molecular (>1000 kDa) water-soluble preparations from different species of two genera *Symphytum* and *Anchusa (Boraginaceae family*) was found to be poly[oxy-1-carboxy-2-(3,4-dihydroxyphenyl)ethylene] or poly[3-(3,4-dihydroxyphenyl)glyceric acid] (PDPGA). The polyoxyethylene chain is the backbone of this polymer molecule and 3, 4-dihydroxyphenyl and carboxyl groups are regular substituents at two carbon atoms in the chain. The repeating unit of this regular polymer is 3-(3, 4-dihydroxyphenyl)glyceric acid residue. This compound is a first representative of a new class of natural polyethers. Then the monomer and methylated derivative of PDPGA were synthesized and their pharmacological properties were compared. The racemic monomer and its virtually pure enantiomers (+)-(2R,3S)-2,3-dihydroxy-3-(3,4-dihydroxy-phenyl)propionic acid [(2R,3S)-DDPPA] and (-)-(2S,3R)-2,3-dihydroxy-3-(3,4-dihydroxyphenyl)propionic acid [(2S,3R)-DDPPA] were synthesized for the first time via Sharpless asymmetric dihydroxylation of trans-caffeic acid derivative using an potassium osmiate catalyst, a stoichiometric oxidant N-methylmorpholine-N-oxide and enantiocomplementary catalysts cinchona alkaloid derivatives (DHQ)2-PHAL and (DHQD)2-PHA as chiral auxiliaries. Methylated derivative of PDPGA was synthesized via ring opening polymerization of 2-methoxycarbonyl-3-(3,4-dimethoxyphenyl)oxirane using a cationic initiator. PDPGA is endowed with intriguing pharmacological activities as anticomplementary, antioxidant, anti-inflammatory, burn and wound healing and anticancer properties. PDPGA and its synthetic monomer exerted anticancer activity in vitro and in vivo against androgen-dependent and androgen-independent human prostate cancer (PCA) cells via targeting androgen receptor, cell cycle arrest and apoptosis without any toxicity, together with a strong decrease in prostate specific antigen level in plasma. However, anticancer efficacy of PDPGA against human PCA cells is more compared to its synthetic monomer. Methylated synthetic analogue of PDPGA did not show any activity against PCA. Overall, this study identifies PDPGA as a potent agent against PCA without any toxicity, and supports its clinical applications.

vbarbakadze@gmail.com