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Caffeic acid-derived polyether from medicinal plants: Structure and biological activity

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A new series of linear and regular 3-arylglyceric acid-derived polyether, namely, poly[oxy-1-carboxy-2-(3,4-dihydroxyphenyl) ethylene] or poly[3-(3,4-dihydroxyphenyl)glyceric acid] (PDPGA) was isolated and identified in the water-soluble, high-molecular weight fractions obtained from extracts of different species of Comfrey. *Symphytum asperum, S. caucasicum, S. officinale, S. grandiflorum* and *Bugloss Anchusa italica*. According to data of 13C, 1H NMR, APT, 2D 1H/13C HSQC, 1D NOE and 2D DOSY experiments, the polyoxyethylene chain is the backbone of the polymer molecule. 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 racemic monomer 2,3-dihydroxy-3-(3,4-dihydroxyphenyl)propionic acid (DDPPA) and its virtually pure enantiomers (+)-(2R,3S)-2,3-dihydroxy-3-(3,4-dihydroxyphenyl)propionic acid and (-)-(2S,3R)-2,3-dihydroxy-3-(3,4-dihydroxyphenyl) propionic acid were synthesized for the first time via Sharpless asymmetric dihydroxylation of trans-caffeic acid derivatives using a potassium osmate catalyst, a stoichiometric oxidant N-methylmorpholine-N-oxide and enantiocomplementary catalysts cinchona alkaloid derivatives (DHQ)2-PHAL and (DHQD)2-PHA as chiral auxiliaries. It is well known that epoxides are valuable synthons in organic synthesis and have been introduced into pharmaceutical applications, such as in the synthesis of antitumor drugs. Subsequently, the building block for the production of derivatives of PDPGA, methyl 3-(3,4-dimethoxyphenyl) glycidate was synthesized based on the Darzen reaction or by oxidation with oxone in order to produce future derivatives of synthetic analogue of natural polymers through ring-opening polymerization of 2,3-disubstituted oxirane. PDPGA is endowed with intriguing pharmacological properties as anticomplementary, antioxidant, anti-inflammatory, burn and wound healing and anticancer properties. PDPGA and DPGA exerted anticancer activity *in vitro* and *in vivo* against human prostate cancer (PCA) cells. However, anticancer efficacy of PDPGA is more effective compared to its synthetic monomer. Overall, this study identifies PDPGA as a potent agent against PCA without any toxicity, and supports its clinical applications.

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