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Poly(sugar acids): Novel acidic polysaccharide poly[3-(3,4-dihydroxyphenyl)glyceric acid] from medicinal plants of Boraginaceae family, its synthetic analogues and their potential therapeutic efficacy

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Abstracts:

Natural polysaccharides have long been studied and widely used in medicine and pharmaceutics. A new polysaccharide is the main chemical constit¬uent of high molecular (>1000 kDa) water-soluble preparations from medicinal plants of Symphytum asperum, S.caucasicum, S.officinale, S.grandiflorum, Anchusa italica, Cynoglossum officinale and Borago officinalis (Boraginaceae) according to data of liquid-state 1H, 13C NMR, 2D 1H/13C HSQC, 2D DOSY and solid-state 13C NMR spectra 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 biopolymer. 3,4-Dihydroxyphenyl and carboxyl groups are regular substituents at two carbon atoms in the chain. The repeating unit of this regular polyether is 3-(3,4-dihydroxyphenyl)-glyceric acid residue. On the other hand PDPGA as a 3,4-dihydroxyphenyl derivative of poly(2,3-glyceric acid ether) belongs to a class of an acidic polysaccharides [poly(sugar acids)] as well. Its basic monomeric moiety glyceric acid is oxidative form of the aldotriose glyceraldehyde. In this case poly(2,3-glyceric acid ether) chain is the backbone of this polymer molecule and 3,4-dihydroxyphenyl groups are regular substituents at 3C carbon atoms in the chain. Every repeating structural unit of PDPGA contains three reactive functional groups, two phenolic hydroxyl groups in ortho-position and one carboxyl group. Multifunctionality of PDPGA should be a reason of its wide spectrum of biological activities. PDPGA exhibited immunomodulatory (anticomplementary), antioxidant, anti-inflammatory, burn and wound healing and anticancer properties. The racemic monomer 2,3-dihydroxy-3-(3,4-dihydroxyphenyl)propionic acid (DDPPA) and its enantiomers (+)-(2R,3S)-DDPPA and (-)-(2S,3R)-DDPPA were synthesized for the first time via Sharpless asymmetric dihydroxylation of trans-caffeic acid derivative using a potassium osmiate catalyst and enantiocomplementary catalysts cinchona alkaloid derivatives (DHQ)2-PHAL and (DHQD)2-PHA as chiral auxiliaries, respectively. These compounds are a new finding in sugar acids. Methylated derivative of PDPGA was synthesized via ring opening polymerization (ROP) of 2-methoxycarbonyl-3-(3,4-dimethoxyphenyl)oxirane using a cationic initiator BF3•OEt2. Oligomers of PDPGA was synthesized by “green” chemistry ROP enzymatic polymerization of methyl 3-(3,4-dibenzyloxyphenyl)glycidate using lipase from Candida rugosa. The size-exclusion chromatography, MALDI-TOF analyses and deprotection showed the formation of oligomers with degree of polymerization up to 5. Enzymatically obtained oligomers of natural polyether cause interest for diverse biological tests. Human Hyaluronidase (Hyal-1) degrades high molecular mass Hyaluronic acid (HA) into smaller fragments which have pro-inflammatory effects. PDPGA possesses the ability to inhibit the enzymatic activity of Hyal-1 completely. Consequently, PDPGA exhibited anti-inflammatory efficacy. PDPGA and its synthetic monomer DDPPA suppressed the growth and induced death in androgen-dependent (LNCaP) and -independent (22Rv1) human prostate cancer (PCA) cells, with comparatively lesser cytotoxicity towards non-neoplastic human prostate epithe-

lial cells PWR-1E. PDPGA induced apoptotic death by activating caspases, and also strongly decreased androgen receptor and prostate specific antigen (PSA) expression. In 22Rv1 xenograft model male athymic nude mice with 22Rv1 xenografts was administered orally of PDPGA. Plasma analyses revealed that PDPGA administration caused a strong dose-dependent decrease in PSA levels by 87%. 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.

Keywords: Biopolymers, polysaccharide, biodegradables, macromoleculars

Conclusion

Thus, our results help establish that one and the same poly[oxy-1-carboxy-2-(3,4- dihydroxyphenyl) ethylene] is the main structural element of both high-molecular water-soluble preparations isolated from the roots of S. asperum and S. caucasicum. Such a caffeic acid-derived biopolymer is hitherto not known and has been identified for the first time. This compound is a representative of a new class of natural polyethers with a residue of 3-(3,4-dihydroxyphenyl)glyceric acid as the repeating unit. We have no information on the biosynthesis of such a polymer in plants, but from the chemical viewpoint, this process can be conceived as the epoxidation of the double bond in caffeic acid followed by the polymerization of the resulting epoxide.

The similarity in the anticomplementary and antioxidant activities of both preparations can obviously be explained by similarity of their chemical nature. At the same time, preparation 2 is somewhat less soluble than 1, which could be due to the higher molecular mass of 2 or fine structural differences not reflected in NMR spectra. The disclosure of these differences (including the determination of the structural importance of residual carbohydrates) and further investigation of the biological activity of the polymers isolated will be the subject of future work. Further study should clarify the physiological function of these polyethers in plants and demonstrate whether their biosynthesis is the unique property of the genus Symphytum or such compounds are also generated in other plants.

Besides, recently it was shown that the new polymers from the roots of S. asperum and S. caucasicum can modulate B-chronic lymphocytic leukaemia (B-CLL) cells apoptosis and cell cycle progression [23,24], therefore these substances can be proposed for further investigations as prospective tumour modulating preparations.

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