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Extended Abstract
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Polymer Congress 2018: A New Class of Caffeic Acid-Derived Biopolyether from Medicinal Plants its Synthetic Basic Monomeric Moiety and their Anticancer Efficacy- Barbakadze V - Tbilisi State Medical University I.Kutateladze Institute of Pharmacochemistry, Tbilisi, Georgia

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Within the field of pharmacologically active biopolymers the area of stable polyethers seems rather attractive. The high-molecular fractions from the several species of two genera Symphytum and Anchusa were isolated by ultrafiltration of water-soluble crude polysaccharides on the membrane filter with cut-off value of 1000 kDa. According to IR, 13C and 1H NMR, 1D NOE, 2D heteronuclear 1H/13C HSQC and 2D DOSY experiments the main structural element of these preparations was found to be a new regular polymeric molecule. 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 caffeic acid-derived polyether, is 3-(3,4-dihydroxyphenyl)glyceric acid residue. Thus, the structure of natural polymer under study was found to be poly [oxy-1-carboxy-2-(3,4-dihydroxyphenyl)ethylene] or poly[3-(3,4-dihydroxyphenyl)glyceric acid] (PDPGA). Such caffeic acid-derived biopolymer to our knowledge has not been known and has been identified for the first time. This compound represents a new class of natural polyethers.

Then the racemic monomer and its 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-dihydroxy-phenyl)-propionic acid [(2S,3R)-DDPPA] were synthesized for the first time via Sharpless asymmetric dihydroxylation of trans-caffeic acid derivatives using an osmium catalyst and (DHQ)2-PHAL and (DHQD)2-PHAL as chiral auxiliaries. 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 -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, our results showed that 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 application.

Ether bonds are found in a wide variety of natural products – mainly secondary metabolites – including lipids, oxiranes, terpenoids, flavonoids, polyketides, and carbohydrate derivatives. Many of these compounds possess different biological activities of pharmacological interest. Within the field of pharmacologically active biopolymers the area of stable polyethers seems rather new and attractive.

The pronounced antioxidant, ant complementary activities and anti-inflammatory property of Symphytum's PDPGA suggested that this phenolic polymer could be a potential antitumor agent. Prostate cancer is one of the most commonly diagnosed cancers among Western men. Among USA men it takes by mortality the second place. The major obstacles in human prostate cancer (PCA) treatment are the development of resistance to androgen ablation therapy leading to hormone-refractory state and the toxicity associated with chemotherapeutic drugs. Thus, the identification of additional nontoxic agents that are effective against both androgen-dependent and -independent PCA is needed. Natural compounds are an important source of anti-cancer drugs, and today there are many natural compounds for therapeutic use of various pre-clinical and clinical tests. Discovering of new natural agents and investigation of their prostate anticancer properties is an actual problem. The comparable efficacy of a novel phytochemical PDPGA, its synthetic racemic monomer DDPPA and methylated derivative of synthetic analogue of PDPGA poly (MDMPO) against androgen-dependent (LNCaP) and androgen independent (22Rv1) PCA cells was studied. The high prostate antitumor effect of natural polymer PDPGA has been determined, which exceeds of the

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synthetic monomer DDPPA [11]. Poly (MDMPO) did not exhibit any anti-cancer efficacy (unpublished results). Both PDPGA and DDPPA suppressed the growth and induced death in PCA cells, with comparatively lesser cytotoxicity towards non-neoplastic human prostate epithelial cells. Furthermore, both PDPGA and DDPPA caused G1 arrest in PCA cells through modulating the expression of cell cycle regulators, especially an increase in cyclin-dependent kinase inhibitors (p21 and p27). In addition, PDPGA and DDPPA induced apoptotic death by activating caspases, and also strongly decreased andogen receptor (AR) and prostate specific antigen (PSA) expression. Consistent with in vitro results, in vivo study showed that PDPGA feeding strongly inhibited 22Rv1 tumors growth by 88% at 5 mg/kg body weight doses, without any toxicity, together with a strong dose-dependent decrease in PSA levels in plasma by 87%; and a decrease in AR and PSA expression but increase in p21/p27 expression and apoptosis in tumor tissues from PDPGA-fed mice.

Conclusion

Thus, the main chemical constituent of water soluble high molecular fractions of different species of Boraginaceous family is one and the same novel caffeic acid-derived polyether PDPGA [3-6]. It inhibited the growth of androgen-dependent and -independent PCA cells both in vitro and in vivo. Results also revealed the broad spectrum effects of PDPGA on AR and PSA levels, cell cycle, and apoptosis revealing some of the plausible underlying mechanisms. Nevertheless, convincing proof for the notion that PDPGA is a promising new tool in PCA management requires a potency comparison with other naturally occurring phenols exemplified by fisetin/quercetin and AR signalling-modulating drugs such as finasteride/dutasteride .

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