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Caffeic Acid-Derived Bio-Polyether from Medicinal Plants – Prospective Therapeutic Agent

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Editorial

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 [1].

The high molecular fractions (HMFs) from different species of genus *Symphytum* (comfrey), prickley comfrey *Symphytum asperum*, Caucasian comfrey *S.caucasicum* (Caucasian endemic), creeping comfrey *S.grtandiflorum* (Georgian endemic), medicinal comfrey *S.officinale* and species of genus *Anchusa*, Italian bugloss *Anchusa italica* (Boraginaceae family) was investigated. The HMFs (>1000 kDa) from above mentioned medicinal plants were obtained by dialysis of hot water extracts followed with ultrafiltration on membrane filter with cut-off value of 1000 kDa [2]. For structure elucidation of their main chemical constituent were used different techniques of nuclear-magnetic resonance (NMR), ^{13}C NMR, APT (Attached proton test), ^{1}H NMR, 1D NOE, 2D $^{1}H/^{13}C$ HSQC, 2D COSY experiments [3-6]. According to data of 2D $^{1}H/^{13}C$ HSQC spectra the correlation between protons and carbon atoms was made. The main chemical constituent of HMFs aforesaid plants was found to be poly[oxy-1-carboxy-2-(3′,4′-dihydroxyphenyl)ethylene or poly[3-(3',4'-dihydroxyphenyl)glyceric acid] (PDPGA) [3-6]. This biopolymer is novel, regular caffeic acid-derived high-molecular (Mr>1000 kDa) polyether.

Polyoxyethylen chain is the backbone of this polymeric molecule. 3,4-Dihydroxyphenyl and carboxylic groups are regular substituents at two carbon atoms in the chain. 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, which contains two aliphatic chiral carbon atoms. The high positive specific rotation $[\alpha]_{D}^{20^{o}C}$= +129.92^{o}(C 0.09%, H_2O) of PDPGA indicated that absolute configuration of chiral centers of PDPGA should be *R,R*.

PDPGA is endowed with intriguing pharmacological properties as immunomodulatary (anticomplementary) [7], antioxidant [7,8] and anti-inflammatory [8] properties.

Afterwards, the racemic and enantioselective synthesis of monomer of PDPGA, namely, 2,3-dihydroxy-3-(3',4'-dihydroxyphenyl)propionic acid (DDPPA) was carried out. This synthesis was realized via Sharpless asymmetric

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dihydroxylation of *trans*-caffeic acid derivatives using the sodium osmiate as catalyst and enantiocomplementary catalysts Cinchona alkaloids derivatives $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL, as chiral auxiliaries. The structures of synthetic compounds were determined by ^1H and ^{13}C NMR spectroscopy [9]. There was not any information on the biosynthesis of PDPGA 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 [3]. Consequently, from this point of view firstly monomer-oxirane 2-methoxycarbonyl-3-(3′,4′-dimethoxyphenyl)oxirane [MDMPO] was synthesized from veratraldehyde (3,4-dimethoxybenzaldehyde, methyl vanillin) and methyl chloroacetate, or by epoxidation of methyl 3-(3′,4′-dimethoxyphenyl) propenoate by oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ - potassium monopersulfate, potassium peroxymonosulfate). Then Methylated derivative of PDPGA poly[2-methoxycarbonyl-3-(3′,4′-dimethoxyphenyl)oxirane] [poly(MDMPO)] was synthesized via ring opening polymerization of MDMPO using a cationic initiator ($BF_3 \cdot OEt_2$). The structure of MDMPG and poly (MDMPG) was identifyed according to data of ^1H, ^{13}C NMR spectra and MALDI-TOF mass-spectrometry [10].

The pronounced antioxidant, anticomplementary 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 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 G_1 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 Boraginaceae 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 signaling-modulating drugs such as finasteride/dutasteride [11].

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