Antitumour activity of synthetic alkyl derivative of protoapigenone in A375 human melanoma cells

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Abstract

Statement of the Problem: Cutaneous malignant melanoma is the most aggressive form of skin cancer, with a high mortality frequency. The alternative therapeutic options involve use of phytochemicals owing to their general acceptance, low side effects and pleiotropic efficacy. Moreover, chemical synthesis represents a tool how to solve the common shortcomings associated with a use of phyto-constituents, such as low stability and poor bioavailability. Enhancement of lipophilicity of a compound by substitution with hydrophobic moiety may also favor its topical/transdermal delivery. Our study presents a pre-clinical assessment of a semisynthetic p-quinol, protoapigenone 1'-O-butyl ether (PABut), in A375 human melanoma cell line also in comparison with natural congener, protoapigenone.

The cytotoxicity was determined using MTT assay. Fluorescence-based methods assisted by flow cytometry were used to asses the levels of reactive oxygen species (ROS) induced by the compounds tested, their influence of cell cycle distribution and apoptosis in melanoma A375 cells. Markers of senescence were evaluated by light microscopy, spectrofluorimetry and by Western blot analysis.

PABut showed a remarkable cytotoxicity against A375 cells comparable to protoapigenone, accompanied by cell cycle arrest in G2/M phase. However, PABut showed a more profound ROS-promoting effect than protoapigenone accompanied by increase of early apoptosis. The selectivity index of PABut was comparable to doxorubicin. Unlike unmodified protoflavone, PABut significantly decreased protein expression of NAD-dependent deacetylase SirT1 and β-actin. This was followed by PABut-induced significant increase of expression of SOD2 enzyme and significant elevation of senescence markers, p21 and p16 proteins and SA-β-Gal.

Conclusion & Significance: These results suggest that PABut exerts high chemotherapeutic potential in melanoma cells involving prooxidant and pro-senescent effect and is suitable for further testing.

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Recent Publications

M Sekelska, A Izsakova, K Kubosova, P Tilandyova, E Csekes, Z Kuchova, M Hyblova, M Harsanyova, M Kucharik, J Budis, T Szemes and G Minarik. Result of Prospective Validation of the Trisomy Test® for the Detection of Chromosomal Trisomies. Diagnostics (Basel). 2019; 9(4). pii: E138. doi: 10.3390/diagnostics9040138.

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Biography

MSc. Erika Csekes is a specialist for clinical diagnostics in Division of Genetics, Medirex ltd. Bratislava, Slovakia. She has an MSc. from Faculty of Natural Sciences Comenius University in Bratislava in the subject Molecular biology. Currently, she is studying for a PhD at Centre of Experimental Medicine Slovak Academy of Sciences, Bratislava within program Biochemistry. She is also a member of Society of Free Radical Research Europe.

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