O17. Anticancer, antioxidant and toxicity activities of new compounds along with their ability to induce hemolysis and methemoglobin formation in human RBCs

Olga Garbuz[1,*], Igor Spinu[2], Oksana Pirvu[2], Iurie Pinzaru[2], Mariana Apostol[2], Valentin Gudumac[3], Aurelian Gulea[1]

[1]Laboratory of Advanced Materials in Biopharmaceutics and Technics, Moldova State University, Chisinau, Republic of Moldova
[2]National Center of Public Health, Chisinau, Republic of Moldova
[3]Laboratory of biochemistry, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

This work represents a series of comparative biological studies of the new synthesized compounds CMJ-23 and CMJ-33 exhibiting selective cytotoxicity.

The antiproliferative effect of these compounds was tested on five cell lines of different origin. It was established that CMJ-23 exhibited cytotoxic activity against cell lines BxPC-3, RD, HeLa, MeW-164 with IC_{50} values of 2.5±2.7; 0.30±0.04; 18.7±1.0; 0.36±0.20 μM, respectively. CMJ-33 showed the highest anticancer activity against cell lines BxPC-3, RD, HeLa, MeW-164 with IC_{50} values of 0.10±0.04; 0.20±0.03; 0.4±0.2 μM, respectively. Comparative study between test compounds and doxorubicin (DOX) in regard to cancer cell lines was showed that CMJ-33 exhibits stronger inhibitory activity on cancer cells proliferation than DOX, and the antiproliferative activity of CMJ-23 are comparable to that of the DOX. An additional experiment aiming on the evaluation of the nephrocytotoxic effect on normal cell line MDCK revealed that CMJ-23 and CMJ-33 are significantly less toxic than DOX.

In order to exclude the eventual presence of concomitant adverse effects associated with oxidative stress, compounds were tested by several antioxidant-capacity (AC) assays. Thus, analyzing the ORAC results was observed that CMJ-23, CMJ-33 showed the highest AC compared with trolox and DOX. Selective ABTS, DPPH - radical scavenging ability of the tested compounds and the standards can be ranked in the order CMJ-23 > CMJ-33 > DOX > trolox > rutin, and CMJ-23 > trolox > rutin > CMJ-33 > DOX, respectively. CMJ-23 and CMJ-33 were more effective in quenching $ABTS^{\bullet+}$ in the system with IC_{50} values of 6.20±0.01 and 11.4±1.4, respectively. The enhanced inhibition displayed on the ABTS radicals shows that the compounds are capable of donating electrons to neutralize free radicals, what indicate their potentials as chemotherapeutic agents for radicals chains terminator.

Drug-induced hemolysis and methemoglobin formation is a relatively rare but serious toxicity liability, so test compounds were performed to screen for toxic hemolysis and methemoglobin formation in human RBCs. This study showed results, which did not exceed the permissible values in the therapeutic concentration range.

Direct toxic evaluation of compounds was performed by Paramecium colorimetric bioassay. It was founded, that the LC_{50} for compound CMJ-23 is 45 times less and for compound CMJ-33 is 24 times less than DOX.

In summary, these results suggest that the tested compounds CMJ-23 and CMJ-33 are of great interest due to their possible use as less toxic and more effective anticancer drugs.

* Corresponding author, tel. +373 691 27 593, e-mail olhamos@mail.ru (Olga Garbuz)