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Effect of Copper Complexes on Human Colon Carcinoma Cell Line and Human Breast Carcinoma Cell Line

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Abstract : Introduction: The continuous demand for new anti-cancer drugs has stimulated chemotherapeutic research based on the use of essential metalloelements with the aim to develop potential drugs with lower toxicity and higher antiproliferative activity against tumors. Copper(II) and its complexes play an important role as suitable species for antiproliferative tests. Objectives: The central objective of the current study was to investigate the potential in vitro anti-proliferative effects of N-salicylidene-L-glutamato copper (II) complexes and molecular mechanism of apoptosis induced by tested complexes. In our project we tested N-salicylidene-L-glutamato copper (II) complexes ZK1 - [Cu(N-salicylidene-L-glutamato)(H2O)2].H2O; MK0 - ([Cu2(N-sal-D,L-glu)2(isoquinoline)2].2H2O); MK1 - [Cu(N-salicylidene-5-methyl-L-glutamato)(H2O)].H2O; MK3 - transbis(ethanol)tetrakis(imidazol)Cu(II)(2+)bis(N-salicylidene-D,L-glutamato-N,O)-KO:KO´-(imidazol); MK5 - [Cu(N-salicylidene-D,L- glutamato)(2-methylimidazol] at concentration range 0.001-100 µmol/L against human colon carcinoma cell line HT-29 and human breast carcinoma cell line MCF-7. Methods: Viability was assessed by direct counting of 0.4% trypan blue dye-excluding cells after 24, 48 and 72 hour cultivations with or without copper complex and by MTT assay. To analyze the type of cell death and its mechanism induced by our copper complex we used different methods. To distinguish apoptosis from necrosis we used electrophoretic analysis, to study the activity of caspases 8 and 9 – luminometric analysis and caspase activity 3 colorimetric assay. Results: The observed anti-proliferative effect of the copper complexes appeared to be dose-, time- and cell line- dependent. Human colon carcinoma cells HT-29 appeared to be more sensitive to the complex MK0 ([Cu2(N-sal-D,L-glu)2(isoquinoline)2].2H2O) than to ZK1 ([Cu(N-salicylidene-L-glutamato)(H2O)2].H2O) and MK1 ([Cu(N-salicylidene-5-methyl-L-glutamato)(H2O)].H2O)). Human colon carcinoma cells HT-29 appeared to be more sensitive to the complex than human breast carcinoma cells MCF-7. IC50 decreased with time of incubation (24, 48 and 72h) for HT-29, but increased for MCF-7. By electrophoresis we found apoptotic cell death induced by our copper complexes in HT-29 at concentrations 1, 10, 50 and 100 µmol/L after 48h (ZK1) and 72h (MK0, MK1) and in MCF-7 we did not find apoptosis. We also studied molecular mechanism of apoptosis in HT-29 induced by copper complexes. We found active caspase 9 in HT-29 after ZK1 ([Cu(N-salicylidene-L-glutamato)(H2O)2].H2O) and MK1 ([Cu(N-salicylidene-5-methyl-L-glutamato)(H2O)].H2O)) influence and active caspase 8 after MK0 ([Cu2(N-sal-D,L-glu)2(isoquinoline)2].2H2O) influence. Conclusion: Our copper complexes showed cytotoxic activities against human colon carcinoma cells HT-29 and breast cancer cell line MCF-7 in vitro. Apoptosis was activated by mitochondrial pathway (intrinsic pathway) in case of ZK1 [Cu(N-salicylidene-L-glutamato)(H2O)2].H2O; MK1 [Cu(N-salicylidene-5-methyl-L-glutamato)(H2O)].H2O; MK3 - transbis(ethanol)tetrakis(imidazol)Cu(II)(2+)bis(N-salicylidene-D,L-glutamato-N,O)-KO:KO´-(imidazol) and MK5 - [Cu(N-salicylidene-D,L- glutamato)(2-methylimidazol] copper complexes and by death receptors (extrinsic pathway) in case of MK0 [Cu2(N-sal-D,L-glu)2(isoquinoline)2].2H2O copper complex in HT-29.

Keywords : apoptosis, copper complex, cancer, carcinoma cell line
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