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Cytotoxic effect of a novel metal Schiff base complex on HepG2 human tumor cells.

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Metal-based compounds show numerous applications in the field of medicine and among these their anticancer effects stand out. Most of the latter are likely due to their binding with DNA, even in the form of non-canonical folding, such as guanine-quadruplexes.[1,2] In this scenario, three Ni(II), Cu(II), Zn(II) complexes of a salphen-like N4-donor ligand were synthesized and their potential cytotoxic effects on HepG2 human hepatocarcinoma cells investigated. First, interesting data emerged from cell viability studies which showed that among the compounds, only the Cu(II) complex exerted a markedly dose-dependent cytotoxic effect at 24 h *vs.* control. Moreover, no significant viability-restraining effect was exerted by either the sole scaffold at all the concentrations tested, or Cu(II) acetate except for the maximum concentration assayed (100 µM). The IC_{50} value at 24 h of the Cu(II) complex was determined and the IC_{50}-treated cells were submitted to a panel of analyses aimed to the evaluation of the biological aspects of cytotoxicity, as reported.[3,4] First, staining with propidium iodide for cell cycle analysis showed the accumulation of treated HepG2 cells in the sub-G_0G_1 fraction without perturbations of the morphological appearance and cell cycle profile, thereby suggesting the occurrence of a higher level of DNA fragmentation, which is associated with cell death. Staining with annexin V-FITC and PI indicated that after exposure the percentage of the viable annexin V-/PI- cells decreased from about 88% of the controls to about 59% and, on the other hand, the percentage of the apoptotic annexin V+/PI+ cells increased from about 6% of the controls to about 35%. The activity of the caspase proteases possibly involved in the cytotoxic effect was tested and the results obtained showed the activation of caspase-3, executor of classical apoptosis, and -5, an inflammatory caspase known to interact with caspase-3 and induce pyroptotic cell death.[5] Interestingly, the increase of the proteolytic cleavage of GSDME protein, a key event in pyroptosis activation, was detected through Western blot. Further, we investigated whether cell exposure could impair the mitochondrial function and cell redox status, demonstrating that the Cu(II) complex induced the dissipation of the mitochondrial membrane potential and the up-regulation of ROS. The preliminary data obtained represent a valuable starting point for the study of the biological mechanisms underlying the potential beneficial effect of the Cu(II) complex on liver tumor cells, so far tested only in vitro, and further studies will be necessary to better define the intracellular pathways targeted by this cytotoxic molecule.

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[3] Abruscato G, et al., *Biology* **2023**; 12:616
[4] Luparello C, et al., *EXCLI J* **2022**; 21:722-743
[5] Wu Y, et al., *J Cell Physiol* **2019**; 234:13571-13581