10th Brazilian Conference on Natural Products
XXXVI RESEM
4-7 November 2025, Belo Horizonte, MG, Brazil

Section: 03

EVALUATION OF LIMONENE ENANTIOMERS AND TWO COPPER(II) COMPLEXES ON CELL VIABILITY AND PROLIFERATION

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Chronic exposure to UV radiation is strongly correlated with the development of skin tumors. In the search for new therapeutic options, nature is a rich source of inspiration, just as coordination compound chemistry has proven to be a strong ally in the new drugs development. One of the challenges in topical treatment of skin cancers is permeation. Limonene, present in many essential oils, is described as a skin permeation enhancer. This study investigated the effects of limonene enantiomers and two copper(II) complexes with the ligands N,N′,N,N'-bis-[2-hydroxy-3,5-di-*terc*-butylbenzyl)(2-piridylmethyl)]-1,3-propanediamine (CuPPN) and N,N′,N,N'-bis-[2-hydroxy-3,5-di-*terc*-butylbenzyl)(2-piridylmethyl)]-ethylenediamine (CuPEN) on the viability and proliferation of human melanoma (SK-MEL-28) and immortalized murine fibroblasts (3T3) cell lines, aiming to propose combinations between limonene and metallic complex. Both *S*-(-)-limonene and R-(+)-limonene did not affect the viability of SK-MEL-28 and 3T3 cells ($IC_{50} \geq 150$ μg/ml) while the CuPEN complex showed greater activity (IC_{50} = 1.1 μg/ml, for both 3T3 and SK-MEL-28) than CuPPN (IC_{50} = 16.2 and 27.5 μg/ml, for 3T3 and SK-MEL-28 cells, respectively). In the clonogenic assay, both complexes showed irreversible antiproliferative effect with significant reduction in colony number (surviving fraction = 29 to 50%) in SK-MEL-28 cells, at concentrations of 1 to 2 μg/ml for CuPEN and 7.5 to 30 μg/ml for CuPPN. Despite the absence of selectivity in cytotoxic effect, in the clonogenic assay both complexes stimulated colony formation in immortalized murine fibroblasts 3T3. The results obtained so far indicate that the CuPEN complex is more potent than the CuPPN complex and that limonene stereoisomerism does not seem to interfere with the effect on cell viability. Future studies are being designed to verify how the combination of limonene, a skin permeation enhancer without cytotoxic effect, with CuPEN and CuPPN complexes will influence the antiproliferative action evidenced for these complexes.

Acknowledgments: CAPES, CNPq, FAEPEX/Unicamp.

Keywords: *Limonene, Copper complexes, Melanoma, Clonogenic assay, Anticancer activity*