ANTITUMOR EVALUATION *IN VITRO* OF NAPHTHOQUINONES MANNICH BASES FOR POSSIBLE TREATMENT OF OSCC

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Introduction

Oral squamous cells carcinoma (OSCC) is the sixth most incident cancer in men worldwide. The survival rate for OSCC is around 5 years. Among the drugs mostly used for the treatment are carboplatin and cisplatin. However, in addition to the high costs of the treatment for nephrotoxicity side effects, acquired resistance have been associated with these chemotherapeutics. Thus, the search for more effective antineoplastic agents is justified. The present study aims to show the synthesis of eighteen synthetic substances from fused naphthoquinones based on Mannich adduct and testing them on OSCC models. A series of experiments were performed *in vitro* on OSCC lines and normal cells, and *in vivo* assays on mice (*Mus musculus*).

Method

Compounds synthesis occurred through the fusion of lawsone to a Mannich reaction (MB1-18). Cytotoxicity and selectivity were evaluated by MTT assays in OSCC (SCC4, SCC9, SCC25) and fibroblast. The following assays were also carried out: hemolysis assays; clonogenic assay; pyknotic nucleus assay**;** caspase inhibitor assay; *in vivo* acute toxicity (CEUA: 982)**;** *in silico* prediction.

Results / Discussion

Among the eighteen 1,4-naphthoquinones tested, only the methyl benzyl (4-chlorophenyl) (3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl) carbamate (MB10) demonstrated a selectivity index higher than 2 (SI: IC_{50} on normal cells / IC_{50} on tumor cells) considering the 3 strains of OSCC (SCC9; SCC4 and SCC25) and normal mouth cells (human fibroblasts). The most selective substance (MB10) reduced the formation of clones in SCC9 via clonogenic assay. The tests for reactive oxygen species (ROS) demonstrated that the substance MB10 did not present a good redox capacity in SCC9. The absence of cell death due to apoptosis was confirmed by tests of pyknotic nucleus and inhibition of caspases. *In vivo* tests showed that the LD_{50} of MB10 was around 150 mg/kg and signs of toxicity were observed in the lungs and kidneys in higher concentrations. Finally, *in silico* predictions of MB10 indicated that its chemical and biological characteristics can provide a good drug profile.

Conclusion

The results indicated that 1 of the 18 Mannich bases synthetic naphthoquinone compounds has a good profile for the treatment of OSCC. Additionally tests are needed to elucidate the type of cell death induced by this substance.

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