Selective cytotoxic activity and apoptosis induction against glioma cell lines by 5-oxygenated-6,7-methylenedioxycoumarins from *Pterocaulon* species

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**Palavras Chave:** Apoptosis; coumarin; Crystal structure; Glioma; Pterocaulon.

**Introduction:** The genus *Pterocaulon* (Asteraceae) encompasses approximately 25 species distributed throughout America, some of them presented cancer-related ethnobotanical uses. The main compounds present in these species are coumarins, these structures can be considered privileged due to their anti-tumorigenic properties. In this context, malignant gliomas are the most common primary central nervous system (CNS) tumors in adults, accounting for 78% of all primary malignant CNS tumors. The glioblastoma multiforme is the most malignant, showing an average survival rate of only 9-12 months. Thus, the present study was designed to evaluate the cytotoxic activity against human (U138-MG) and rat (C6) glioma cell lines by 5-oxygenated-6,7-methylenedioxycoumarins from *Pterocaulon* species and evaluate the selective cytotoxic effect on glioma cell cultures using as models of non-tumor neural cells.

**Experimental:** Aerial parts of *Pterocaulon balansae* Chodat and *P. lorentzii* Malme were collected in South Brazil, and voucher specimens were deposited in the herbarium of the UFRGS (ICN 140003 and 140001). For compound [1], the X-ray data were collected an *Enraf-Nonius Kappa-CCD* diffractometer. The human glioblastoma cell line U138-MG and the rat glioma cell line C6 were obtained from ATCC and assessment of glioma cell viability was evaluated by MTT method. Apoptotic cells were quantified by annexin V–FITC–propidium iodide (PI). Data are expressed as mean ± S.D. and analyzed for statistical significance by one-way analysis of variance (ANOVA) followed by post-hoc for multiple comparisons (Tukey test).

**Results and Discussion:** The coumarins 5-methoxy-6,7-methylenedioxycoumarin [1] 5-(3-methyl-2-butenyloxy)-6,7-methylenedioxycoumarin [2] and 5-(2,3-dihydroxy-3-methylbutoxy)-6,7-methylenedioxycoumarin [3] isolated from *Pterocaulon* species showed significant cytotoxicity against two glioma cell lines. Compound [1] presented IC\(_{50}\) values of 34.6 μM and 31.6 μM against human (U138-MG) and rat (C6) glioma cells, respectively, being at least two times more cytotoxic than compounds [2] and [3]. This result can be explained by the planar conformation adopted by the molecule [1], which is due to a non-classical hydrogen bond between a hydrogen of the methoxyl and the oxygen of the methylenedioxy groups, determined by X-ray diffraction studies (Cambridge Crystallographic Data Centre 779123). The present work has also shown the ability of 5-oxygenated-6,7-methylenedioxycoumarins to induce apoptosis without causing necrosis in glioma cells. Another important finding was that the cytotoxic effect induced by [1] in glioma cells was not observed in the organotypic cultures, indicating selective cytotoxicity for tumoral cells.

**Conclusion:** 5-(3-methyl-2-butenyloxy)-6,7-methylenedioxycoumarin presented an excellent and selective cytotoxic activity against glioma cell lines. This structure represents a potential hit the medicinal chemistry further medicinal chemistry investigations.

**Financial:** This work was supported by CAPES and CNPq. Vianna were the recipients of a CAPES Post-doctoral fellowship (Project PNPD, number 2683091).