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PTERODON EMARGINATUS VOGEL OLEORESIN CO-LOADED WITH DOXORUBICIN IN pH-SENSITIVE NANOCAPSULES AS POTENTIAL THERAPY FOR BREAST CANCER

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Nanocarriers have emerged as a promising strategy for the delivery of bioactive natural products with low hydrophilicity, enabling targeted tissue distribution with greater specificity. Therefore, this study aimed to develop multifunctional nanocapsules capable of co-delivering natural anti-inflammatory and antitumor agents along with chemotherapeutics, with the goal of enhancing efficacy, specificity, and safety. The phytochemical profile of *Pterodon emarginatus* Vogel oleoresin was determined using gas chromatography (GC) and liquid chromatography (HPLC) coupled with mass spectrometer. Conventional and PEGylated nanocapsules were prepared via nanoprecipitation method and stored at 4°C for stability assay. The mean diameter and polydispersity index were determined by dynamic light scattering and zeta potential was associated with electrophoretic mobility. The encapsulation content was evaluated by centrifugation-ultrafiltration, where nonencapsulated doxorubicin and total were analyzed by spectrophotometry. *In vitro* release profile was obtained by dialysis method, using Hepes buffer pH 7.4 and 5.0, as acceptor compartment, at 37°C under agitation. The amount of doxorubicin released from nanocapsules was measured by HPLC. Cell viability (4T1 tumor and fibroblasts cells) was assessed by the Sulforhodamine B assay. While antitumor efficacy and toxicity *in vivo* were evaluated in 4T1 tumor-bearing mice. Diterpenes and sesquiterpenes were identified in the oleoresin. Conventional and PEGylated nanocapsules oleoresin-loaded with or without doxorubicin were monodisperse (polydispersity index <0.1) with a size of less than 150 nm and negative zeta potentials (-30 mV). The nanocapsules remained stable over a 30-day period, maintaining their original physicochemical properties. Encapsulation efficiency was greater than 90%, with release modulated by pH medium. *In vitro* data showed high selectivity and improved cytotoxicity against tumor cells for PEGylated nanocapsules oleoresin-loaded combined with doxorubicin. Additionally, *in vivo* data showed not only increased efficacy but also reduced toxicity

to liver and heart tissue and less body weight loss. Therefore, the results presented in this paper show that *Pterodon emarginatus* Vogel oleoresin co-loaded with doxorubicin in PEGylated nanocapsules can be considered a promising system for the tumors treatment. The authors thank the support from their institutions and CAPES, CNPq and FAPEMIG for their financial support.

Keywords: *Pterodon emarginatus, PEGylated nanocapsules, doxorubicin, antitumor activity, drug delivery, natural products*