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IN VITRO AND IN VIVO ANTI-INFLAMMATORY POTENTIAL OF THE ENDOPEROXIDE SESQUITERPENE 3,6-EPIDIOXI-BISABOLA-1,10-DIENE-(EDBD) FROM DRYMIS BRASILIENSIS.

Bruno Antonio Ferreira[1*]; Taís de Campos Lima[2]; Isabella Silva Cassimiro[2]; Danielle Reis Napolitano[2]; Eric Umehara[1]; **Felipe da Silva Sales[1]**; João Henrique Ghilardi Lago[1]; Fernanda de Assis Araújo[3].

felipe.sales@ufabc.edu.br

1- Centro de Ciências Naturais e Humanas - Universidade Federal do ABC, São Paulo. Brasil. 2 - Departamento de Fisiologia, Instituto de Ciências Biomédicas – Universidade Federal de Uberlândia, Minas Gerais, Brasil. 3 - Laboratório de Fisiologia – Universidade Federal de São João del-Rei - Campus Centro-Oeste Dona Lindu, Minas Gerais, Brazil.

Plants of the genus *Drimys* (Winteraceae), including *D. brasiliensis*, are rich sources of specialized metabolites, such as sesquiterpenes with anti-inflammatory activity. The aim of this study was to evaluate the *in vitro* and *in vivo* anti-inflammatory potential of the endoperoxide sesquiterpene 3,6-epidioxi-bisabola-1,10-diene (EDBD), obtained from the hexanic extract of *Drimys brasiliensis* branches. Using Raw 264.7 macrophages, we evaluated the cytotoxicity of this sesquiterpene through the MTT assay, as well as its ability to inhibit the production of nitric oxide after stimulating the cells with LPS and zymosan (Griess method). The *in vivo* tests consisted of using the sponge implant model in C57BL/6 mice (CEUA/UFU - protocol number 23117.042533/2024-32). A sponge disc was aseptically implanted in the back of each of the 40 mice used in this stage of the study. The animals were treated daily with intraimplant injections containing 0.1, 1 or 10 µg of EDBD, solubilized in 10 uL of 0.5% DMSO solution, or with the vehicle alone (control group). On the 9th day after surgery, the animals were euthanized and the implants were collected, weighed and processed for biochemical analysis. Neutrophil and macrophage infiltrates near the sponge implants were indirectly assessed by measuring the activity of the enzymes myeloperoxidase (MPO) and N-acetyl-β-D-glucosaminidase (NAG), respectively. Our results showed low cytotoxicity associated with EBDB treatment (IC50 ≈ 200 µg/mL) and the compound's ability to inhibit nitric oxide production in stimulated macrophages. In the *in vivo* tests, the activities of MPO and NAG enzymes were reduced in the animals that receiving daily injections containing 1 or 10 µg of the sesquiterpene. Our results showed the anti-inflammatory potential of this compound both *in vitro* and *in vivo*. The authors thank the support from their institutions and the financial support of CNPq (152604/2024-3), CAPES (finance code 001), FAPEMIG and FAPESP.

Keywords: *natural products; sesquiterpenes; inflammation; chronic inflammation; sponge model.*