

TITLE: ANTI-INFLAMMATORY ACTIVITY OF B-CARYOPHYLLENE COMBINED WITH DOCOSAHEXAENOIC ACID IN A MODEL OF SEPSIS INDUCED BY *Staphylococcus aureus* IN MICE

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ABSTRACT:

Sepsis is a set of serious organic manifestations caused by an infection, whose progression culminates in exacerbated inflammation and oxidative stress, poor prognosis, and high hospital costs. Antioxidants have been evaluated against sepsis, among them, essential oils, such as β -caryophyllene (BCP) and polyunsaturated fatty acids, such as Docosahexaenoic Acid (DHA). The aim of the study was evaluate the anti-inflammatory activity of the association of these two compounds. To determine the anti-inflammatory dose, 48 male Balb/c mice were used in the Carrageenan (Cg)-induced peritonitis assay, with subcutaneous administration of BCP and/or DHA. The evaluation of the inflammatory condition occurred through the migration of neutrophils to the peritoneum and local nitric oxide dosage. Later, a pathophysiological test was performed with 32 male Balb/c mice, in which the animals were inoculated with *Staphylococcus aureus*, euthanized after 24 or 48 hours, and from them, fluids and tissues (spleen, heart and lung) were extracted, on which were performed: total and differential count of leukocytes, cytokines dosage, histological and bacterial analyses. Statistical analysis was performed using the Kruskal Wallis and Mann-Whitney tests and Dunn's post-test, considering p-value <0.05. Treatment with BCP-DHA, at a dose of 200 μ L/animal, inhibited, significantly, the migration of neutrophils in a Cg-induced peritonitis model. After *S. aureus* infection, in the groups treated with BCP-DHA there was a significant decrease in the total and differential count of leukocytes; increased expression of cytokines TNF- α and IFN- γ in treated groups, rise of IL-4 and IL-5 in treated and infected and treated groups and augment of IL-6 and IL-12 groups in infected and treated groups. Histological and bacterial analysis revealed lower neutrophil migration and lower bacterial load, respectively, in the infected and treated groups. In general, the BCP-DHA association presented anti-inflammatory activity against two different models of acute inflammation and infection and may become a possible therapeutic adjuvant in sepsis.

Keywords: Sepsis. β -caryophyllene. Docosahexaenoic acid. Anti-inflammatory. *Staphylococcus aureus*.

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