

**TITLE:** ANTI-INFLAMMATORY ACTIVITY OF  $\beta$ -CARYOPHYLLENE ASSOCIATED WITH DOCOSAHEXAENOIC ACID IN SEPSIS MODEL 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, worse prognosis and high hospital costs. Antioxidants have been evaluated against sepsis, among them, essential oils, such as  $\beta$ -caryophyllene (BCP), and polyunsaturated fatty acids, such as Docosahexaenoic Acid (DHA). The objective of this study was to 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, and the evaluation of the inflammatory condition occurred through the migration of neutrophils to the peritoneum and local nitric oxide dosage. Later, the 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 were extracted fluids and tissues (spleen, heart and lung), on which were performed: total and differential count of leukocytes, cytokines dosage, histological and bacterial analyzes. Statistical analysis was performed using the Kruskal Walli and Mann-Whitney tests and Dunn's post-test, considering p-value <0.05. Treatment with BCP-DHA, at a dose of 200  $\mu$ 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 significative decrease in the total and differential count of leukocytes; increased expression of cytokines TNF- $\alpha$  and IFN- $\gamma$  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 analyzes 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 as a possible therapeutic adjuvant in sepsis.

**Keywords:** sepsis, anti-inflammatory,  $\beta$ -caryophyllene, docosahexanoic acid, *Staphylococcus aureus*.

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