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BRAZILIAN RED PROPOLIS AND ISOLATED PRENYLATED BENZOPHENONES AS POTENTIAL ANTI-INFLAMMATORY MODULATORS MODULATING NETs *AND CYTOKINES*

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Previous studies have consistently reported the anti-inflammatory potential of compounds isolated from propolis, yet the mechanisms underlying these effects remain incompletely understood. Among the pathways involved in inflammation, neutrophil extracellular traps (NETs) formation and the release of pro-inflammatory cytokines are considered crucial events contributing to tissue damage and disease progression. To the best of our knowledge, this is the first study to evaluate the capacity of prenylated benzophenones isolated from Brazilian red propolis, as well as the crude extract, to modulate NETs release and cytokine production in human neutrophils. Human neutrophils were isolated from peripheral blood and pre-treated with guttiferone E, oblongifolin B, or the crude ethanolic extract of Brazilian red propolis for 1 hour at concentrations ranging from 100 to 0.03 µM. Cells were subsequently stimulated with 5 µM ionomycin to induce NET formation. NET release was quantified for 6 hours post-stimulation using SytoxGreen® as DNA extracellular probe, and cytokine levels were determined at the final time point. Treatment with higher concentrations (100 and 30 µM) of both isolated compounds and the crude extract resulted in a significant reduction in NET release compared to controls. Furthermore, the same concentrations were associated with decreased secretion of pro-inflammatory cytokines TNF-α and IL-1β, suggesting a dose-dependent inhibitory effect (oblongifolin B: reduced 67% TNF in the highest dose, and 60% in IL-1B; gutifferone B: reduced 45 % TNF in the highest dose, and a modest 5% in IL-1B; crude extract: reduced both TNF and IL-1B in 55% in the highest dose). These findings indicate that both isolated prenylated benzophenones and the whole extract of Brazilian red propolis possess relevant anti-inflammatory properties through the modulation of neutrophil activity. Importantly, these data highlight a potential mechanism of action that could contribute to the therapeutic effects attributed to propolis in inflammatory disorders. Nevertheless, additional studies are warranted to further characterize this concentration-dependent effect, to evaluate possible cytotoxicity in neutrophils, and to validate the results in *in vivo* models. Such investigations will be essential to support the pharmacological development of red propolis-derived compounds as potential anti-inflammatory agents.

Keywords: *Brazilian Red Propolis, Prenylated Benzophenones, NET, cytokines, anti-infammatory*