III SIMPÓSIO INTERNACIONAL EM INVESTIGAÇÕES QUÍMICO-FARMACÊUTICAS
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I CONGRESSO LUSO-BRASILEIRO DE CIÊNCIAS E TECNOLOGIAS EM SAÚDE

Área: FAR 50

SAFETY EVALUATION AND MODULATORY EFFECTS ON INNATE IMMUNE RESPONSE OF PYRAZOLINE DERIVATED COMPOUNDS

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INTRODUCTION

Inflammation is a form of defense against tissue damage or pathogens entry. Although being essential for the homeostasis, this process must be stopped, avoiding this way its exacerbation. Non-steroidal anti-inflammatory drugs play an important role to stopping the inflammation, despite having many adverse effects. Pyrazolines are molecules characterized by having a five-membered heterocycle with high structural versatility, presenting many biological activities such as antioxidant, anti-inflammatory, among others. Therefore, this study aims to evaluate the safety and pharmacological parameters using *in silico* methods and immunomodulatory potential of pyrazoline compounds identified as PH0, PH3, PH4 and PH7.

MATERIAL AND METHODS

A predictive pharmacological and toxicological evaluation was performed *in silico*, using the SwissADME and Qsar Toolbox platforms. To evaluate its anti-inflammatory potential, different methodologies were performed, such as dosage of nitric oxide (NO), pro-inflammatory cytokines levels (IL-1β and TNF, ELISA), and a chemotaxis and efferocytosis assays were performed.

RESULTS

The *in silico* analysis show that all compounds have good pharmacological characteristics such as a molecular weight lower than 500 g/mol, PH0 and PH7 has shown a good probability to be orally absorbed, different from PH3 and PH4, due to the presence of a chloride in its structure. In the toxicological in silico analysis using the Qsar Toolbox software PH3 and PH4 has shown alerts to carcinogenicity. The other compounds showed negative predictive results. The nitric oxide (NO) measurement, in macrophages and neutrophils stimulated with LPS, showed significantly decrease for all compound, with PH4 showing the highest inhibition rates. The ELISA analysis showed that PH4 promote a decrease in the TNF levels, with a higher average inhibition. The chemotactic assay was performed just with PH4, considering that it presented the best initial results, and also showed satisfactory results regarding *in vitro* chemotaxis of neutrophils. In the efferocytosis assay, only PH0, PH3 and PH4 seems to have similar and positive activity on this resolution mechanism of inflammation. On the supernatant of the efferocytosis assay, the levels of the anti-inflammatory IL-10 cytokine were measured, showing that only PH3 compound had promising effects when it comes to the resolution of the inflammatory process.

CONCLUSIONS

Together, the results herein obtained shown the promising effects of PH3 and PH4, but further analyzes will be performed to determine if these two compounds have potential to go to in vivo rodent tests.

ACKNOWLEDGMENTS

CAPES, CNPq, INCT-Inovamed, FAPESC, UNIVALI.