RESUMO SIMPLES - PRODUTOS NATURAIS E BIOATIVOS DE INTERESSE FARMACOLÓGICO

MODULATION OF INFLAMMATORY PATHWAYS BY URSOLIC ACID AND OLEIC ACID IN ANIMAL MODELS OF WOUND HEALING: A SYSTEMATIC REVIEW

Rafael França Lima (rafael.franca@discente.ufma.br)

Larissa Rodrigues De Sousa (larissa.rodrigues1@discente.ufma.br)

Giovana Maria Silva Lima (giovana.lima@discente.ufma.br)

Amanda Tissore Forwille Reis (tissoreforwille@gmail.com)

Marcelo Souza De Andrade (marcelo.andrade@ufma.br)

Maria Do Socorro De Sousa Cartágenes (cartagenes.maria@ufma.br)

Introduction: Wound healing restores tissue integrity after injuries through coordinated inflammatory, proliferative, and remodeling phases. Fibroblasts are essential for granulation tissue formation and extracellular matrix deposition. Disruptions in these processes may result in delayed healing or fibrosis, generating significant health impacts. Therefore, plant-derived bioactive compounds have emerged as promising therapeutic alternatives due to their pharmacological potential. In this context, improving wound healing remains a

clinical challenge, and natural compounds represent valuable sources of chemical innovation and drug development.

Objective: To evaluate the effects and molecular mechanisms of ursolic acid and oleic acid on inflammatory pathway modulation during wound healing in predominantly mice and rat models.

Methods: This systematic literature review was conducted according to PRISMA guidelines and registered in PROSPERO. The guiding question was structured using the PICO framework: "What are the effects of ursolic acid and oleic acid on wound healing in animal models?" Electronic searches were performed in PubMed and Web of Science using the MeSH terms ("ursolic acid" AND [inflammation OR "wound healing"]) and ("oleic acid" AND [inflammation OR "wound healing"]). Original articles published in the last five years, written in English, available in full text, and conducted in in vivo animal models were included. Reviews, theses, conference abstracts, and studies without a clearly described methodology were excluded. Study selection was independently performed by two reviewers in two stages, with disagreements resolved by consensus.

Results: The analyzed studies demonstrated that the biological effects of ursolic acid and oleic acid on wound healing depend on their chemical characteristics and the cellular microenvironment. Overall, ursolic acid promoted an anti-inflammatory, antioxidant, and immunomodulatory response, contributing to a tissue environment favorable for repair, whereas oleic acid exhibited context-dependent effects, with isolated administration or certain lipid combinations promoting a predominantly pro-inflammatory response. These findings were predominantly observed in mice and rat models. Mechanistically, oleic acid activated the TLR4/MYD88/NF-?B signaling pathway, increasing the production of TNF-a, IL-1ß, IL-6, IL-8, COX-2, and PGE2. In contrast, ursolic acid inhibited NF-?B phosphorylation, reducing TNF-a, IL-1ß, and IL-6 expression, suppressing Th17-related cytokines (IFN-?, IL-17A, IL-21, IL-23, and TGF-ß), enhancing antioxidant defenses through Nrf2 and HO-1 activation, decreasing iNOS and CD68 expression, and promoting immune rebalancing by reducing macrophage and neutrophil infiltration while increasing CD4? and CD8? T

lymphocytes, NK cells, and dendritic cells. Biphasic homeostatic responses characterized by transient cytokine fluctuations were also reported.

Conclusion: Ursolic acid and oleic acid modulate inflammation through distinct molecular mechanisms, mainly involving the TLR4/MYD88/NF-?B and Nrf2/HO-1 signaling pathways. Ursolic acid consistently exhibits anti-inflammatory, antioxidant, and immunomodulatory properties, whereas oleic acid exerts context-dependent inflammatory effects. These findings highlight the therapeutic potential of both compounds, particularly ursolic acid as promising bioactive agents for developing innovative strategies to improve wound healing. Nevertheless, additional preclinical studies and well-designed clinical trials are required to validate their safety, efficacy, and translational application in tissue repair.

Palavras-chave: ursolic acid; oleic acid; inflammation; wound healing; systematic review.