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Anti-Inflammatory and Anti-Metastatic Effects of Herbal Extracts on the HIF-1α/COX-2/MMP-2 axis in Triple-Negative Breast Cancer Cells

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ABSTRACT

Triple-negative breast cancer (TNBC) remains a major clinical challenge due to its aggressive nature and lack of targeted therapies. In this study, we investigated the effects of three medicinal plant extracts—*Alchemilla smirnovii* Juz., *Rumex obtusifolius*, and *Inula helenium*—on inflammatory and metastatic markers in MDA-MB-231 human TNBC cells. MDA-MB-231 cells were treated with *Alchemilla smirnovii* Juz., *Rumex obtusifolius*, and *Inula helenium* extracts under $CoCl_2$- and TNF-α-induced conditions. Protein expression of HIF-1α, COX-2, and MMP-2 was assessed using Western blot and immunocytochemistry. Cytotoxicity was evaluated by MTT assay. Using $CoCl_2$-induced hypoxia and TNF-α-stimulated inflammation models, we assessed the modulation of the HIF-1α/COX-2/MMP-2 signaling axis. MTT assays confirmed that the extracts, at 0.5 mg/mL, did not exhibit cytotoxicity after 24–72 hours. Western blot analysis revealed that all three extracts significantly downregulated HIF-1α, COX-2, and MMP-2 expression under both basal and stimulated conditions. Notably, *A. smirnovii* and *R. obtusifolius* demonstrated the most potent inhibitory effects under TNF-α stimulation, while *A. smirnovii* and *I. helenium* were most effective under $CoCl_2$-induced hypoxia. Immunocytochemistry confirmed these findings, showing decreased fluorescence intensity of COX-2 and MMP-2 and no signs of nuclear condensation, supporting the non-cytotoxic nature of the treatments. These results suggest that the tested plant extracts exert strong anti-inflammatory and anti-metastatic effects without inducing cell death, making them promising candidates for adjunctive therapy in TNBC. Their ability to suppress key pro-tumorigenic markers involved in extracellular matrix remodeling and angiogenesis could help prevent cancer cell invasion and dormancy. This study highlights the therapeutic potential of plant-derived compounds in modulating tumor-associated pathways in breast cancer and supports further investigation of these extracts in combination with conventional chemotherapy.

Keywords: herbs, triple-negative breast cancer, inflammation, metastasis

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