Treat Chronic Lymphedema: The Effects of Apigenin, Diosmetin, and Chicoric Acid on TNF-Alpha and COX-2 Levels of Stimulated RAW 264.7 Macrophages

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Lymphedema is chronic, progressive and potentially disabling, characterized by regional bodily swelling and accumulation of protein-rich interstitial fluid. It affects over 100 million people worldwide. Lymphedema causes chronic cutaneous inflammation, attracting phagocytic macrophages to the region. Poor tissue conditions created by impaired circulation and stagnant interstitial fluid depress macrophage activity. There is no pharmacological or curative treatment for lymphedema. This in-vitro experiment was conducted to develop a first natural pharmaceutical to treat chronic lymphedema by determining the anti-inflammatory and immune-modulating effects of apigenin, diosmetin, and chicoric acid when applied to stimulated RAW 264.7 murine macrophages, measuring Tumour Necrosing Factor alpha (TNFa) and Cyclooxygenase-2 (COX-2). After a 48-hour exposure, all reagents demonstrated an immune-stimulating effect, shown by an increase in TNFa. Diosmetin caused a significant immune-stimulating effect, with TNFa levels above the “High LPS Stimulation” control. The role of lymphangiogenesis in the setting of lymphedema is a prime area of investigation. An experiment with mouse tail models of lymphedema revealed that an inhibition of COX-2, along with a paradoxical stimulation of TNFa (and correlated rise in VEGF-C), reduced lymphedema, improving the lymphatic circulatory insufficiency associated with inflammation. Therefore, this experiment was undertaken to find a natural reagent that would stimulate macrophage TNFa expression while influencing COX-2 expression. All reagents showed potential; however, diosmetin’s significant ability to enhance TNFa in this experiment demonstrates the promise of a future breakthrough in developing a drug to treat chronic lymphedema.

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