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The Impact of *Hypericum alpestre* and *Rumex obtusifolius* on Proline Metabolism in Breast Cancer Model Animals

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ABSTRACT

Proline levels are known to increase in different types of cancer cells, correlating with the processes of proliferation and invasiveness. Inhibition of the proline biosynthesis enzymes, has been shown to reduce tumor cell growth and enhance the cytotoxicity of chemotherapeutic drugs. Therefore, targeting proline biosynthesis represents a promising therapeutic approach for cancer treatment. The aim of the research is to investigate the effect of *Hypericum alpestre* and *Rumex obtusifolius* extracts on proline levels in various organs, including tumor cells, of breast cancer model animals. Additionally, we evaluated the combined effects of herbal extracts with the inhibitors L-NAME (N^G-nitro-L-arginine methyl ester) and nor-NOHA (N^{ω}-hydroxy-L-norarginine), which inhibit nitric oxide synthase and arginase, respectively-two enzymes indirectly involved in proline biosynthesis through metabolic intermediates. Our results showed that proline levels significantly increased in various organs of DMBA inducing cancer-bearing animals. However, treatment with the herbal extracts—either alone or in combination with L-NAME and nor-NOHA—led to a suppression of proline biosynthesis in both tumors and other organs, with varying degrees of effectiveness. The most effective combinations observed in our study were *H. alpestre* + **nor-NOHA** and *H. alpestre* + **L-NAME**. L-NAME acts as an arginase inhibitor. Since arginase is involved in the production of ornithine, a precursor in proline biosynthesis, its inhibition reduces ornithine formation. Consequently, this may limit proline and collagen synthesis, contributing with a reduction in tumor size. The combinations of herbal extracts and metabolic enzyme inhibitors show potential as promising candidates for the development of novel cancer therapies aimed at targeting proline metabolism.

Keywords: proline, tumor, *Hypericum alpestre, Rumex obtusifolius*

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