

“Honorary Biomedical Sciences & Health Information Lecture Series”



THE POTENTIAL OF NATURAL LACTATE DEHYDROGENASE INHIBITORS FOR CANCER THERAPY

A Distinguished Lecture

By

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Abstract: A characteristic feature of aggressive malignancy is the overexpression of lactic acid dehydrogenase- (LDH-) A, concomitant to the pericellular accumulation of lactate. The elevated levels of lactic acid are associated with the heightened rate of glucose consumption with dominant reliance on substrate level phosphorylation rather than oxidative phosphorylation to produce ATP. In a cancer cell, the accelerated glycolytic activity is typically indicative of a metabolic response to the lack of oxygen (O₂), but in cancer cells, this pattern occurs in the presence or absence of O₂ with an accumulation of lactic acid (Warburg effect). In a recent high-throughput screening, we identified *Rhus chinensis* (Mill.) gallnut (RCG) (also known as *Galla Chinensis*) extract as a potent (IC₅₀ < 1 µg/mL) inhibitor of human LDH-A (hLDH-A). In this study, through bioactivity guided fractionation of the crude extract, the data demonstrate that penta-1,2,3,4,6-O-galloyl-β-D-glucose (PGG) was the primary constituent responsible for hLDH-A inhibition, present at ~9.95 ± 0.34% dry weight. Theoretical molecular docking studies of hLDH-A indicate that PGG acts through competitive binding at the NADH cofactor site, effects confirmed by functional enzyme studies where the IC₅₀ = 27.32 nM was reversed with increasing concentration of NADH. Moreover, we confirm protein expression of hLDH-A in MDA-231 human breast carcinoma cells and show that PGG was toxic (LC₅₀ = 94.18 µM), parallel to attenuated lactic acid production (IC₅₀ = 97.81 µM). In a 72-hour cell proliferation assay, PGG was found to be a potent cytostatic agent with the ability to halt cell division (IC₅₀ = 1.2 µM) about paclitaxel (IC₅₀ < 100 nM). In summary, these findings demonstrate that PGG is a potent hLDH-A inhibitor with significant capacity to halt the proliferation of human breast cancer cells.

Keywords: Warburg Effect, acidity, tumor, lactic acid, hypoxia, mitochondria, OXPHOS, lactic acid dehydrogenase

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