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Cardamonin inhibits breast cancer growth by repressing HIF-1α-dependent metabolic reprogramming

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Abstract

Background: Cardamonin, a chalcone isolated from *Alpiniae katsumadai*, has anti-inflammatory and anti-tumor activities. However, the molecular mechanism by which cardamonin inhibits breast cancer progression largely remains to be determined.

Methods: CCK-8 and Hoechst 33258 staining were used to detect cell growth and apoptosis, respectively. HIF-1α driven transcription was measured by luciferase reporter assay. Glucose uptake and lactate content were detected with 2-NBDG and L-Lactate Assay Kit. Cell metabolism assays were performed on Agilent's Seahorse Bioscience XF96 Extracellular Flux Analyzer. Mitochondrial membrane potential was measured with JC-1 probe. DCFH-DA was used to measure ROS level. Protein expression was detected by western blotting assay. Immunohistochemistry was performed to measure the expression of HIF-1α, LDHA and CD31 in tumor tissues.

Results: Cardamonin inhibited growth of the triple negative breast cancer cell line MDA-MB-231 in vitro and in vivo by suppressing HIF-1α mediated cell metabolism. Cardamonin inhibited the expression of HIF-1α at mRNA and protein levels by repressing the mTOR/p70S6K pathway, and subsequently enhanced mitochondrial oxidative phosphorylation and induced reactive oxygen species (ROS) accumulation. We also found that cardamonin inhibited the Nrf2-dependent ROS scavenging system which further increased intracellular ROS levels. Eventually, accumulation of the intracellular ROS induced apoptosis in breast cancer cells. In addition, cardamonin treatment reduced glucose uptake as well as lactic acid production and efflux, suggesting its function in repressing the glycolysis process.

Conclusions: These results reveal novel function of cardamonin in modulating cancer cell metabolism and suppressing breast cancer progression, and suggest its potential for breast cancer treatment.

Keywords: Cardamonin, Breast cancer, Mitochondrial oxidative phosphorylation, Reactive oxygen species, Apoptosis, Cell metabolism

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