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**PhD Dissertation Defense**

Entitled

*MOLECULAR MECHANISM OF ACTION OF A NATURAL POLYPHENOLIC COMPOUND AND P300 INHIBITOR "CARNOSOL" AGAINST THE TRIPLE NEGATIVE BREAST CANCER*

by

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https://eu.bbcollab.com/guest/6e1ca69391cc44b3b4e13003e27abaad

Abstract

Carnosol, a naturally occurring phytopolyphenol found in sage, oregano and rosemary, has been extensively studied by our laboratory for its anticancer effects in various types of cancer. In human triple negative breast cancer (TNBC), carnosol was shown, to inhibit cellular viability, colony growth, induced cell cycle arrest, autophagy, and apoptosis. Nonetheless, very little is known about molecular mechanism of action. In the current study, the ability of carnosol to inhibits metastasis and tumor growth was examined. Wound healing and invasion assays revealed that carnosol inhibited migration and invasion at non-cytotoxic concentrations of MDA-MB-231 cells. We also found that carnosol inhibited the activity and downregulated the expression of MMP-9. Activation of STAT3, transcription factor that regulate MMP-9 expression, was also inhibited via carnosol-mediated ROS-dependent proteasome degradation. *In vivo* study using chick embryo tumor growth assay has showed that carnosol significantly and markedly suppressed tumor growth and metastasis of breast cancer xenografts. We also found that carnosol targeted p300 and PCAF histone acetyl transferases (HATs) to proteasome degradation through a ROS-dependent mechanism. Interestingly, using a cell-free system, we show for the first time that carnosol efficiently and selectively inhibited histone acetyltransferase activity of p300 while having no effect on the other HATs such PCAF or GCN5. This work provide further confirming that carnosol represents a promising anti-breast cancer therapeutic compound and identifies it as a novel natural p300 inhibitor that could be added to the existing panel of inhibitors.

**Keywords:** TNBC, metastasis, tumor growth, STAT3, ROS, UPR, p300, acetyltransferase activity.