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Entitled

DECIPHERING THE MOLECULAR MECHANISM THROUGH WHICH RHUS CORIARIA EXERTS ITS ANTI-CANCER ACTIVITY

By

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Abstract

Cancer remains a major health problem around the globe. Among various types of treatments, plants have been shown to have great capacity in cancer treatment, one of which, is *Rhus coriaria*. Commonly known as sumac, *R. coriaria* is a culinary herb that is known to possess different therapeutic values including anti-oxidant and anti-microbial activities. In this study, we tested the effect of *Rhus coriaria* extract (RCE) on the migration, invasion and metastasis of the triple negative breast cancer cells MDA-MB-231. We showed that non-cytotoxic concentrations of RCE inhibited migration and invasion, blocked adhesion to fibronectin and downregulated MMP-9 and prostaglandin E2. RCE also decreased the adhesion of MDA-MB-231 cells to Human Umbilical Vascular Endothelial Cells (HUVECs) and inhibited the transendothelial migration of MDA-MB-231 cells through HUVECs. Additionally, we found that RCE inhibited angiogenesis, reduced VEGF production. The suggested mechanism of action of RCE appears to be through inhibiting NFκB, STAT3 and nitric oxide (NO) pathways. In the second part of the thesis, we extended our study and investigated the anti-cancer effect of RCE on HT-29 and Caco-2 human colorectal cancer cells. We found that RCE inhibited the viability and colony growth of colon cancer cells. RCE also induced Beclin-1-independent autophagy and caspase-7-dependent apoptosis. The suggested mechanism through which RCE exerts its effect is by inactivating AKT/mTOR pathway and downregulating Beclin-1, p53 and procaspase-3 through targeting them to proteasome-dependent degradation. Pretreating the cells with MG-132, a proteasome inhibitor, restored these proteins to level comparable to control cells and reduced RCE-induced cell death and blocked the activation of autophagy and apoptosis. Proteasomal degradation of mTOR, which occurred 3 hours after treatment with RCE was concomitant with an overall increase in proteins ubiquitination which target the proteins for degradation by the proteasome. In conclusion, these preliminary results make *Rhus coriaria* a promising chemopreventive and therapeutic candidate against both breast and colon cancer.

Keywords: *Rhus coriaria*, breast cancer, colon cancer, apoptosis, autophagy, proteasome.