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Entitled

*ANTI-CANCER ACTIVITY OF RHUS CORIARIA (SUMAC)
AGAINST 5-FLUOROURACIL-RESISTANT COLORECTAL CANCER CELLS*

by

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Abstract

Colorectal cancer (CRC) is the second leading cause of cancer-related death, both worldwide and in UAE. 5-fluorouracil (5-FU), a pyrimidine analogue, is a chemotherapeutic agent that is an integral component of chemotherapy regimens for CRC treatment. However, 5-FU resistance (intrinsic and/or acquired) inhibits their clinical efficacy. In recent years, there has been a growing popularity for plant-based cancer therapeutics, specifically using phytochemical compounds. *Rhus coriaria* (Sumac) is a Mediterranean plant whose fruits are used as a spice and medicinal herb. Extracts of *Rhus coriaria* fruits have been reported to exhibit anticancer activity against breast and CRC cancers. In the present study, the anti-cancer activity of RCE against 5-FU-resistant CRC was investigated using *in vitro* models of 5-FU-sensitive (HCT-116) and 5-FU-resistant CRC (5-FU-HCT-116). Firstly, two regional varieties, Jordanian and Lebanese, of RCEs were tested and both inhibited the proliferation of HCT-116 and 5-FU-HCT-116 cells; however, the Lebanese extract was found to be more potent and used for subsequent analysis. RCE inhibited the formation and growth of HCT-116 and 5-FU-HCT-116 colonies. Additionally, RCE induced autophagy, as evidence by cytoplasmic vacuolation and expression of autophagy markers (p62 and LC3BII) through degradation of autophagy regulators mTOR and STAT3. RCE also induced DNA damage-mediated apoptosis as evidenced by γ H2AX and cleaved PARP accumulation. Further, RCE induced caspase 7-dependent apoptosis in HCT-116 cells; however, the mechanism of apoptosis induction in 5-FU-HCT-116 was unclear, suggesting a non-canonical pathway. Additionally, fractions of RCE were tested and the bioactive fractions were identified. Collectively, these findings confirm that RCE exerts potent anticancer activity against 5-FU-resistant CRC and is a promising source for phytochemicals that can potentially be used for the treatment of 5-FU-resistant CRC.

Keywords: Phytochemicals, Colorectal Cancer, 5-Fluorouracil, Drug Resistance, Autophagy, Apoptosis

