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Anti-cancer Activity of *Rhus coriaria* (Sumac) Extracts against 5-Fluorouracil Resistant Colorectal Cancer

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Background and aims: Colorectal cancer (CRC) is the second leading cause of cancer-related death in the UAE. 5-Fluorouracil (5-FU), a pyrimidine analogue, is the most common chemotherapeutic agent used for the treatment of CRC; however, intrinsic or acquired 5-FU resistance inhibits its clinical efficacy. Hence, development of alternative treatments to overcome 5-FU resistance in CRC is necessary. In recent years, phytochemicals have been investigated as potential anti-cancer drugs in preclinical and clinical studies. Extracts of *Rhus coriaria* (RCEs) or tanner's sumac, a plant native to the Mediterranean region, are rich in numerous phytochemical compounds and have a broad spectrum of pharmacological properties including antioxidant and anti-inflammatory properties. Although the anti-cancer effect of RCE has been reported in CRC, its anti-cancer effect on 5-FU-resistant CRC has not been investigated. Therefore, herein, we investigated the anti-cancer effect of two regional variations of RCE on 5-FU-resistant CRC.

Methods: 5-FU-resistant and -sensitive CRC cells were treated with varying concentrations of RCEs for 48 h, and subjected to cytotoxicity assay, colony formation assay, and western blot analysis. Additionally, the chemical profiles of the two RCEs were analyzed by LC-MS/MS.

Results: Both RCEs significantly inhibited the proliferation of 5-FU-resistant CRC cells in a time- and dose- dependent manner; this inhibition was comparable to that of 5-FU-sensitive CRC cells. With both RCEs, the effect on proliferation was more pronounced in 5-FU-sensitive CRC cells. Moreover, RCE inhibited the colony formation ability of both 5-FU-resistant and -sensitive CRC cells, and consistent with the cytotoxicity assay, the effect was more pronounced in 5-FU-resistant CRC cells as indicated by complete abrogation of colony formation at a low concentration (200 µg/mL). Microscopic examination of CRC cells following RCE treatment revealed cytoplasmic vacuolation suggestive of autophagy as well as apoptotic bodies. Consistent with these findings, western blot analysis revealed that RCE induces a dose-dependent increase in the expression and accumulation of autophagy marker LC3B and apoptosis marker cleaved-PARP in both 5-FU-resistant and -sensitive HCT116 cells. Lastly, LC-MS/MS analyses of the two RCEs revealed that they have different chemical profiles.

Conclusions: Development of alternative treatments to overcome 5-FU resistance in CRC is of urgent need. Our findings suggest that RCEs, namely RCE-K, have potent anticancer

activity and are promising sources for phytochemicals that can potentially be used as therapeutic agents for 5-FU resistant CRC. In future studies, the signaling pathways involved in the observed effects will be investigated, and the two RCEs will be fractionated to identify the active fraction and novel phytochemical compounds that are responsible for the observed anti-cancer activity.