Anticancer effects and mechanisms of Zuo-Jin-Wan and its alkaloidal ingredients in vitro and in mice

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Abstract

Background and Aims: Hepatocellular carcinoma (HCC) is ranked fifth in cancer incidence worldwide. In Taiwan, HCC is one of the top two leading causes of cancer death. There is as yet no proven effective medical therapy for treating HCC. Traditional Chinese medicine has been used in cancer treatment or as an adjuvant therapy for cancer treatment for centuries, but there is little scientific evidence on its effectiveness. The aim of this study was therefore to investigate the anticancer effects and molecular mechanisms of Zuo-Jin-Wan, its components (Coptis chinensis and Evodia rutaecarpa), and its major alkaloidal ingredients (berberine and evodiamine) in human hepatoma HepG2 cells and tumor-bearing mice.

Materials and Methods : For in vitro studies, HepG2/NF-κB/luc cells were treated with Zuo-Jin-Wan, Coptis chinensis, Evodia rutaecarpa, berberine, and evodiamine for 48 hours at TC50 doses and the total RNA was collected for microarray analysis. For in vivo studies, the HCC xenograft model in immunocompromised mice was established by direct intrahepatic injection of HepG2/NF-κB/luc cells into mice. Three days after tumor cell implantation, mice were imaged on 7, 14, or 28 days after daily treatment with Zuo-Jin-Wan (200 mg/kg) or PBS and sacrificed to examine therapeutic effects of Zuo-Jin-Wan.

Results and Conclusions: The TC50 values of Zuo-Jin-Wan, Coptis chinensis, Evodia rutaecarpa, berberine, and evodiamine were 7.7, 4.3, 320, 5.9, and 0.3 μg/mL, respectively. Hierarchical cluster analysis revealed that Coptis chinensis shared a similar gene expression profile with Zuo-Jin-Wan, suggesting that Coptis chinensis may be the main component responsible for the anticancer effects of Zuo-Jin-Wan. Network analysis showed that c-myc played a central role in the network topology. For the in vivo studies, our data showed that on 7 days after treatment, statistically significant decreases of tumor ascitic fluid and tumor weight/liver weight ratio were observed in Zuo-Jin-Wan group mice compared to control mice. In conclusion, Zuo-Jin-Wan, its components and its major alkaloidal ingredients significantly suppressed tumor growth in HepG2 cells in vitro and in HepG2 tumor-bearing mice. Moreover, c-myc played a critical role in the anticancer effect of Zuo-Jin-Wan. Our data not only provide scientific evidence for the anticancer effects of Zuo-Jin-Wan on liver cancer but also provide useful guidelines to Traditional Chinese Medicine doctors for the treatment of HCC.