Synergistic Enhancement Of Cytotoxicity Of Known Chemotherapeutic Agents By Mahanine In Colon And Cervical Carcinoma

Abstract of thesis

We have concentrated on the development of novel combined regimes using a herbal agent, mahanine, a carbazole alkaloid from the edible Indian medicinal plant Murraya koenigii to reduce the concentration-limiting toxicity of a few clinically approved chemotherapeutics (5-FU, cisplatin and paclitaxel). Moreover, we have demonstrated the mechanistic insight regulated by the treatment of these combined agents.

In this thesis, we established that mahanine synergistically potentiates the growth-inhibitory activity of 5-FU, cisplatin and paclitaxel and significantly reduces their concentrations. We have found that mahanine sensitizes colon cancer cells to 5-FU-induced cytotoxicity. The cell growth inhibitory concentrations of 5-FU were decreased ~4-7 fold in presence of mahanine to achieve same percentage of growth inhibition. Furthermore, mahanine synergistically augments the cytotoxicity of cisplatin and paclitaxel even at ~5-8 and ~3-5 fold reduced concentration respectively in cervical cancer cells.

We also demonstrated that mahanine induces apoptosis through reactive oxygen species (ROS) generation in colon cancer cells. It activated tumour suppressor proteins PTEN and p53/p73 through mahanine-induced ROS leading to their accumulation in nucleus. Furthermore, mahanine in combination with 5-FU showed the ability to enhance ROS generation which subsequently increased PTEN and p53/p73 proteins and suppressed chemo-migration. In cervical cancer, mahanine inhibited JAK1 and Src and subsequently promoted proteasome-mediated degradation of STAT3. Mahanine-mediated suppression of JAK1 and Src might play a significant role in the inhibition of phosphorylation of STAT3. Moreover, the combination of mahanine and cisplatin induced enhanced inhibition of STAT3 activation, cell migration and increased apoptosis of cervical cancer cells compared to single agent.

Taken together, this thesis work significantly imparts that mahanine may be a prospective agent to reduce the concentration of 5-FU, cisplatin and paclitaxel in adjunct for the treatment of cancers and thereby decreasing its toxicity.

Attested

06/04/2015