Abstract Title: Corilagin, a promising complimentary herbal agent for ovarian cancer therapy

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BACKGROUND: Chinese herbal medicine has been recognized as an important part in Integrative therapy, it has a contribution to make at every stage in the treatment of cancer, not just the symptoms. Cancer survivors with unmet needs were more likely to use complementary and alternative herbal medicine, not only in the east countries, but also in the west countries. Here we introduce a promising complimentary anti-cancer herbal agent – Corilagin.

Phyllanthus urinaria L. and *P. emblica* L. have traditionally been used as anti-inflammatory and hepatoprotective folk medicines in China and India. Recently, much attention has been paid to their anti-tumor activities. We have identified that Corilagin is a major anti-tumor active component extracted from Phyllanthus niruri L. Our previous works found that Corilagin inhibited the growth of ovarian and hepatocellular cancer cells via several signaling pathways that are essential for cancer cells proliferation and survival, such as: inhibition of TGF-β/AKT/ERK pathways, activation of p53-p21Cip1-cdc2/cyclin B1 pathways.

HYPOTHESIS: Corilagin may have a complimentary effects with chemo-drugs in ovarian cancer treatment.

METHODS: Three ovarian cancer cell lines (Hey, SKOv3ip, HO8910PM) were treated by different concentration of Corilagin , paclitaxel or carboplatin; single or combinated. Cell proliferation was checked by Sulforhodamine B (SRB) and 3D culture staining. Lysates from untreated and treated cancer cells were used for Reverse phase protein array (RPPA) analysis at The University of Texas, M.D. Anderson Cancer Center RPPA Core Facility. Signaling changes were examined by Western blot.

RESULTS: Corilagin distinctly increased inhibition effects of paclitaxel or carboplatin ($p<0.001$ in all concentrations), specially at lower doses of these two chemo-drugs. In RPPA analysis, it showed that both paclitaxel and carboplatin treatment upregulated several apoptotic and death proteins (Caspase 3, Caspase 7, PDCD4…), while combined with Corilagin, these apoptotic effects were enhanced. Meanwhile, Corilagin presented different pathways with paclitaxel and carboplatin, it inhibited the expression of Snail, PLK1, DUSP4, ERA1, RB1, MDM2…, and enhanced the expression of E2F1, HIF1A, NDRG1… Western blots results further confirmed that Corilagin could inhibit Snail and phosphate-ERK expressions, elevate E-cadherin expression in ovarian cancer cells, but paclitaxel or carboplatin did not show inhibition to Snail and also not to phosphate-ERK expressions. All these changes suggested that Corilagin acts not only via apoptotic pathways, but also via its distinct Snail pathways. As we knew, Snail is a key inducer of epithelial-mesenchymal transition (EMT), plays an important role in ovarian cancer metastasis. Snail was significantly higher in ovarian cancer metastatic lesions, and its expression correlated with the stage of ovarian cancer. The inhibition of Snail by Corilagin , but not by paclitaxel or carboplatin, suggested this is a critical mechanism of chemo-drugs sensitization. Corilagin is an herb medicine with lower toxic effects to normal cells, especially hepatoprotective, it could provide as an ideal complimentary medicine when combinating with highly toxic chemo-drugs.