

Current therapies for metastatic prostate cancer are only marginally effective, and hence novel treatment modalities are urgently needed. Considerable evidence suggests that chronic inflammation plays a pivotal role in the development and progression of prostate cancer. Thus agents that can suppress these inflammatory mediators could form the basis of novel therapy for prostate cancer patients. In our study, we focused on analyzing the potential anticancer effects of nimbolide, a terpenoid lactone derived from *Azadirachta indica* (Neem tree) against prostate cancer. **METHODS** Molecular biology techniques such as western blot analysis, DNA binding, luciferase assays, and immunohistochemistry were used for both *in vitro* and *in vivo* experiments. **RESULTS** Data from the *in vitro* studies indicated that nimbolide could inhibit cell proliferation, induce apoptosis and suppress cellular invasion and migration. Interestingly, nimbolide also abrogated the activation of pro-inflammatory STAT3 transcription factor, and this effect was found to be mediated via an increased production of reactive oxygen species (ROS), whereas depletion of ROS attenuated p-STAT3 inhibitory effects of the drug. The *in vivo* efficacy of nimbolide was also noted in transgenic adenocarcinoma of mouse prostate (TRAMP) model, in which this triterpenoid significantly suppressed the tumor progression and growth without exhibiting any substantial adverse effects. **CONCLUSION** Overall our findings indicate that nimbolide exhibits significant anticancer effects in prostate cancer, and these effects may be mediated at least in part through the modulation of STAT3 signaling pathway.

**Key words:** prostate cancer; nimbolide; STAT3; ROS

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## Ascochlorin overcomes chemoresistance and regulates the plasticity of doxorubicin induced EMT via modulation of the NF- $\kappa$ B pathway in hepatocellular carcinoma

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**Abstract:** **OBJECTIVE** Doxorubicin-based therapy has been found to be not significantly effective for the treatment of advanced stage hepatocellular carcinomas (HCCs), which often undergo epithelial-mesenchymal transition (EMT) during tumor progression. Increasing evidence suggest(s) that epithelial cell transformation to mesenchymal state can enhance the ability to self-renew and confer greater resistance to the conventional chemotherapeutic drugs. The aim of this study was to examine the potential efficacy of ascochlorin, an isoprenoid antibiotic to overcome drug resistance induced by doxorubicin in HCC cell lines and to elucidate its underlying mechanism(s) of action. **METHODS** The effect of doxorubicin and ascochlorin on HCC cell lines was determined by MTT, Western blotting, immunofluorescence and NF- $\kappa$ B DNA binding assays. **RESULTS** Our results indicate that HCC cells that show a mesenchymal-like phenotype, are resistance to the doxorubicin therapy which directly correlated with an increased slug expression. We also observed that activation of NF- $\kappa$ B pathway plays an essential role in doxorubicin induced-chemoresistance and pharmacological inhibition of this pathway with ascochlorin can significantly reverse drug-induced invasion/migration and resistance in HCC cells. **CONCLUSION** Our results indicate that combination treatment of doxorubicin with ascochlorin has the potential to inhibit HCC growth

and metastasis.

**Key words:** doxorubicin; ascochlorin; chemoresistance; EMT; NF- $\kappa$ B; HCCP

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## Garcinol sensitizes human head and neck carcinoma to cisplatin in a xenograft mouse model despite downregulation of proliferative biomarkers

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**Abstract:** **OBJECTIVE** Platinum compounds such as cisplatin and carboplatin are frequently used as the first-line chemotherapy for the treatment of the head and neck squamous cell carcinoma (HNSCC). In the present study, we investigated whether garcinol, a polyisoprenylated benzophenone can chemosensitize HNSCC to cisplatin. **METHODS** The effect of garcinol and cisplatin on HNSCC was assessed by MTT, Western blotting, real time PCR, FACS, immunohistochemistry, DNA binding assay and xenograft mouse model. **RESULTS** We found that garcinol inhibited the viability of a panel of diverse HNSCC cell lines, enhanced the apoptotic effect of cisplatin, suppressed constitutive as well as cisplatin-induced NF- $\kappa$ B activation, and downregulated the expression of various oncogenic gene products (cyclin D1, Bcl-2, survivin and VEGF). *In vivo* study showed that administration of garcinol alone (0.5 mg·kg<sup>-1</sup>, ip five times/week) significantly suppressed the growth of the tumor, and this effect was further increased by cisplatin. Both the markers of proliferation index (Ki-67) and microvessel density (CD31) were downregulated in tumor tissues by the combination of cisplatin and garcinol. The pharmacokinetic results of garcinol indicated that good systemic exposure was achievable after ip administration of garcinol at 0.5 and 2 mg·kg<sup>-1</sup> with mean peak concentration ( $c_{\max}$ ) of 1825.4 and 6635.7 nmol·L<sup>-1</sup> in the mouse serum, respectively. **CONCLUSION** Overall, our results suggest that garcinol can indeed potentiate the effects of cisplatin by negative regulation of various inflammatory and proliferative biomarkers.

**Key words:** HNSCC; chemoresistance; NF- $\kappa$ B; proliferation; garcinol

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