Letter

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Attenuation of tumor growth by honokiol: An evolving role in oncology

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ABSTRACT: *Honokiol may exert significant anti-neoplastic effects in other systemic tumors besides skin cancers by virtue of modulation of other pathways. For instance, honokiol attenuates tumor growth in mammary malignancies. It mediates its anti-neoplastic role in these tumors by accentuating the phosphorylation of AMPK. As a result, honokiol causes significant mitigation of tumor proliferation and growth.*

Guillermo *et al*. have provided great insight into the role of honokiol in management of skin cancers (*1*). Honokiol may exert significant anti-neoplastic effects in other systemic tumors besides skin cancers by virtue of modulation of other pathways.

Honokiol attenuates tumor growth in mammary malignancies. It mediates its anti-neoplastic role in these tumors by accentuating the phosphorylation of 5' adenosine monophosphate-activated protein kinase (AMPK). AMPK in turn affects the pACC-pS6K pathway (*2*). Nitric oxide (NO) levels are also significantly attenuated. Nuclear factor kappa B (NF-κB) activity is also reduced by honokiol. Besides this, honokiol also augments cytoplasmic translocation of liver kinase B1 (LKB1) resulting in attenuated invasiveness as well as migration of the cancer cells. As a result, honokiol causes significant mitigation of tumor proliferation and growth. Intracellular cGMP levels are also decreased markedly (*3*). Besides these effects honokiol also causes inhibition of cyclooxygenase-2. Interestingly, honokiol also exhibits synergism with chemotherapeutic agents such as rapamycin by accentuating the inhibition of the PI3K/Akt/mTOR pathway (*4*).

Similar effects are seen in gastric carcinomas. Honokiol administration results in attenuated activation of the signal transducer and activator of transcription 3 (STAT3) pathway (*5*). It mediates this effect by up-regulating SPH-1. Honokiol also augments calpain-II-mediated cleavage of GRP94 thus augmenting intra-tumoral apoptosis (*6*). Simultaneous decrease in intra-tumoral production of VEGF is also seen. As a result, intra-tumoral angiogenesis is markedly decreased. Honokiol also decreases growth in colorectal malignancies. It mediates this role by modulating the Notch pathway (*7*). Doublecortin-like kinase 1 (DCLK1) expression is markedly down-regulated. Besides this inhibition of γ-secretase is also seen. These effects are especially more pronounced when honokiol is used in conjunction with ionizing radiation. In fact, honokiol increases the radio-sensitivity of colorectal cancer cells. Hes-1 levels are also attenuated (*8*). APH-1 is also decreased. Cyclin D1 expression is down-regulated while the Bax/Bcl-2 ratio is increased. Similar effects are seen in pancreatic malignancies. It mediates this role by increasing p27 levels. On the other hand, Cdk4 expression is down regulated. This results in attenuated IκB-α phosphorylation as well as augmented accumulation of NF-κB in the cytoplasm of the cancerous cells (*9*). Honokiol especially augments and increases the anti-proliferative and apoptotic effects of other chemotherapeutic agents such as gemcitabine.

As is evident from the above examples honokiol exerts significant anti-neoplastic activity in a number of systemic tumors. Hopefully, the coming few years will see increased use of honokiol for mitigating tumor growth.

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