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Inhibitory effects of dihydrohinokiflavone on tumor cell growth and invasion

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Matrix metalloproteinases (MMPs) inhibitors were screened from Metasequoia glyptostroboides and one potent inhibitor, dihydrohinokiflavone (DHHF), a biflavonoid, was selected. DHHF inhibited proliferation of HT1080, human fibrosarcoma cells in a dose-dependent manner. Noncytotoxic levels of DHHF dramatically decreased MMP-9 and MMP-2 production in unstimulated cells, but did not change the level of tissue inhibitor of metalloproteinase (TIMP)-1, an inhibitor of MMP-9. DHHF further inhibited phorbol 12-myristate13-acetate (PMA)-induced MMP-9 overproduction and proMMP-2 activation. In HT1080 cells, which express wild-type p53 and Rb, DHHF treatment induced G1 cycle arrest. The G1 arrest in cell cycle progression was associated with a marked decrease in cdk2, cdk4, and phospho-Rb. DHHF increased the levels of p53, a key protein for cell cycle arrest and overexpression of mutant p53 blocked the growth inhibitory effect of DHHF. These results indicate that DHHF inhibits cell growth through p53-dependent pathways. DHHF inhibited critical mediators for cell survival, Akt, phospho-Akt, and Bcl-2. This inhibition was associated with MMP-9 downregulation and partly responsible for G1 arrest. Furthermore, DHHF upregulated phospho-JNK, a key factor for cell death, and increased cell death susceptibility in the presence of hydrogen peroxide. DHHF showed marked inhibition of *in vitro* HT1080 and B16F10 melanoma cell growth, invasion and motility, and further was effective to inhibit *in vivo* tumor growth. All these

results suggest that DHHF can be a good therapeutic compound for anti-tumor including chemoprevention and anti-invasion.