Starvation of tumor - chemopreventive intervention of angiogenic switch to control cancer

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The growth and progression of solid tumors requires angiogenesis. Tumor angiogenesis requires the proliferation of existing endothelial cells in the tumor microenvironment. The growth of solid tumors beyond ~2 mm diameter depends upon the vascularization of the tumor by the recruitment of microvessel. This process includes endothelial cell growth, proliferation, invasion, migration and tubular organization resembling the microvessel. Interruption of any of these processes can suppress tumor angiogenesis. It is basically regulated by the balance between pro-angiogenic and anti-angiogenic factors. Tumor cells secrete angiogenic factors, including vascular endothelial growth factor (VEGF) and cytokines to generate a vascular microenvironment. These angiogenic factors initiate inflammatory and angiogenic mechanisms including cell signaling through autocrine and paracrine regulation of tumor and endothelial cells. Recently, we observed that many phytochemicals including silibinin, fisetin, acacetin, decursin, etc, have potential to inhibit more than one process of angiogenesis. These chemopreventive agents inhibit human endothelial cell growth, cell cycle progression, survival as well as matrigel invasion and migration. They also inhibit angiogenesis in chorioallantoic membrane assay and matrigel implants in mice. Matrix metalloproteinase (MMP-2) activity, that supports cell invasion and migration, was also inhibited in endothelial and cancer cells. In animal tumor models, the anti-tumor effect was associated with the inhibition of tumor angiogenesis. In lung cancer studies, we identified inducible nitric oxide synthase (iNOS) as an important molecular target of silibinin efficacy. iNOS is known to induce VEGF level as well as tumor angiogenesis. In prostate cancer, it has inhibited tumor growth, progression and metastasis together with tumor angiogenesis. These studies suggest that naturally occurring small molecules/phytochemicals have both anticancer as well as antiangiogenic activities, and thus such compounds could be potentially utilized for the control of tumor growth and progression.