# INHIBITION OF PROGESTIN-INDUCED VEGF IN MAMMARY CANCER BY CURCUMIN AND 2-METHOXY ESTRADIOL AND THEIR POTENTIAL ROLE AS ANTI-ANGIOGENIC & CHEMOPREVENTIVE COMPOUNDS

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## ABSTRACT

Estrogen/Progestin combined hormone replacement therapy (HRT) is commonly prescribed to alleviate the symptoms of menopause in women. Combination HRT however is associated with an increased risk of breast cancer, an effect that has been attributed to the progestin component, the most common of which is medroxyprogesterone acetate (MPA). It is likely that breast cancers arise due to progestin-dependent release, from breast tumor cells, of vascular endothelial growth factor (VEGF), a potent angiogenic growth factor. In the present study I show that curcumin, a turmeric root derivative, and 2-methoxyestradiol (2ME2), a natural metabolite of estradiol, effectively inhibit progestin-induced VEGF secretion from breast cancer cells in vitro. Furthermore, curcumin delays progestin-accelerated DMBA-induced tumorigenesis in Sprague-Dawley rats. 2ME2 inhibits hypoxia inducible factor -1{alpha} (HIF-1$\alpha$) and also prevents progestin-dependent VEGF release from tumor cells, suggesting that HIF-1$\alpha$ is an essential transcription factor for mediating the effects of progestins on VEGF elaboration. YC-1, a specific HIF-1$\alpha$ inhibitor, blocks both the progression of DMBA-induced progestin-accelerated mammary tumors in Sprague-Dawley rats and progestin-dependent human breast cancer xenografts in nude mice, confirming the importance of HIF-1$\alpha$ in progestin-dependent VEGF release from tumor cells. YC-1 also blocks progestin-induced increases in DNA binding of HIF-1$\alpha$ to the VEGF promoter in human tumor cells. We conclude that curcumin, 2ME2 and YC-1 show promise as chemotherapeutic and chmopreventive compounds for hormone-dependent mammary cancers.