

THERAPEUTIC AND CHEMOPREVENTIVE POTENTIAL OF LUTEOLIN
AGAINST GROWTH AND METASTASIS OF BREAST CANCER

Matthew T. Cook

Dr. Salman M. Hyder, PhD, Dissertation Supervisor

DISSERTATION ABSTRACT

Breast cancer is the second leading cause of cancer-related death in older women. Many postmenopausal women undergo hormone replacement therapy (HRT) with estrogen and progestin to alleviate the symptoms of menopause. Recent studies implicate the progestin component of HRT as being most likely responsible for elevated breast cancer risk and increased mortality.

We examined the ability of luteolin (LU), a naturally-occurring flavonoid found commonly in fruits and vegetables, to both prevent the onset of breast cancer, and inhibit breast tumor growth and metastasis. To examine the preventative potential of LU we utilized a progestin (P)-accelerated 7,12-dimethylbenz(a)anthracene (DMBA)-induced rat model of mammary cancer and found that LU prevents tumorigenesis dose-dependently. Immunohistochemical (IHC) analysis of mammary tissue showed that LU exerts suppressive effects on P-induced intratumoral vascularization.

Using a P-dependent breast cancer xenograft nude mouse model we examined the therapeutic efficacy of LU. The flavonoid effectively blocks P-driven tumor growth in T47-D human breast cancer cells, IHC analysis demonstrating that LU disrupts intratumoral vascularization. In vitro studies in T47-D cells showed that LU induces apoptosis and blocks P-induced stem cell-like enrichment.

Progestins not only increase the risk of breast cancer in postmenopausal women but have also been implicated in driving their metastatic potential. To address such a situation we employed a hormone-independent xenograft model of lung metastasis utilizing triple-negative breast cancer cells (TNBC), since most hormone-dependent cancer cells ultimately become hormone-resistant and lose therapeutic markers. LU significantly reduced the formation of lung colonies arising from TNBCs, with minimal to no animal toxicity, and in vitro suppressed migration of TNBCs. These studies provide compelling evidence that LU possesses chemopreventative, therapeutic, and anti-metastatic properties which might be harnessed to combat breast cancer.