Title
Antitumorigenic Effects of Flaxseed and Its Lignan, Secoisolariciresinol Diglycoside (SDG)

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Flaxseed

The flax plant (*Linum usitatissimum*) is an annual herb believed to have originated in Egypt. The plant's fibers are used to make linen cloth, and its oil, also known as linseed oil, has many industrial uses. The seeds are also one of the richest dietary sources of phytoestrogens, estrogenic compounds derived from plants. Phytoestrogens are divided into three main classes, isoflavononones, coumestans, and lignans. Isoflavones are found predominantly in legumes, such as soybeans. Coumestrol is found mainly in alfalfa and clovers. Lignans are the most ubiquitous phytoestrogens because they are involved in plant cell wall formation. Plant lignans can be converted to the mammalian lignans, enterolactone and enterodiol, in the colon by bacterial fermentation from their plant precursors, secoisolariciresinol and matairesinol, respectively. [4,9] All bind to the estrogen receptor, and evidence exists to support both partial agonism and antagonism at these receptors. [4] Because flaxseed is the richest dietary source of lignans, it has been used to investigate the potentially anticarcinogenic effects of lignans in animal studies and some human trials.

Flaxseed and lignans in animals

The majority of the animal studies on flaxseed's antitumorigenic effects have been done by Lilian Thompson and her lab group at the University of Toronto. Additional work in men with prostate cancer has been carried out by Wendy Demark-Wahnefried *et al* of Duke University. In a series of experiments with flaxseed, flaxseed oil, and flaxseed's lignan, secoisolariciresinol diglycoside (SDG), Thompson's group determined that antitumorigenic effects of flaxseed observed in vitro with mammary and colon carcinogenesis could be attributed specifically to SDG. [2, 12-14] Proposed mechanisms to date for the observed inhibition of tumor growth have included estrogenic and antiestrogenic effects, anti-oxidative effects, antiproliferative and anti-aromatase effects. [10]

Li *et al* collaborated with Thompson on an experiment of SDG dietary supplementation in a model of melanoma metastasis by intravenous injection of murine melanoma cells in suspension into mouse tail veins. This study was a follow-up to a previous study in which they demonstrated that dietary supplementation with flaxseed reduces metastasis of melanoma cells in mice. The follow-up study investigated SDG as the effector molecule in flaxseed in preventing melanoma metastases using the tail vein injection model, with the number of pulmonary tumors, as well as the size and volume, used as the indices of metastatic disease. Three groups of mice were given escalating doses of SDG, with a control group receiving no SDG. The mice with the highest two SDG doses showed a significant decrease in the number of mice per group that had greater than 50 lung metastases. The SDG supplementation also reduced the volume and cross-sectional area of the tumors in a dose-dependent manner, with significant results again for the two higher doses. [10]

In an *in vitro* experiment with human breast cancer cell lines, Chen and Thompson attempted to define a potential mechanism for the observed inhibition of metastasis. They examined the effect of escalating doses of enterodiol and enterolactone on adhesion to basement membrane proteins by non-estrogen-sensitive breast cancer cells, as well as cell 'invasiveness' through a gel matrix containing basement membrane proteins. While their experimental design seemed a plausible assay for the variables

examined, their results among the dose groups did not show a titrated response, which discredits their conclusion that enterodiol and enterolactone inhibit metastasis by blocking binding to ECM proteins and basement membrane proteins. [3] Further studies to examine the exact mechanism of the potential inhibition of metastasis are necessary.

Thompson's group also explored dietary flaxseed as combined therapy with tamoxifen in an estrogen-dependent human breast cancer line. Tamoxifen is an adjuvant therapy for breast cancer, particularly estrogen-receptor positive (ER+) cancers. Some tamoxifen resistance has been noted after prolonged treatment, as well as menopausal-like symptoms due to its antiestrogenic effects. Patients have reported taking soy or flaxseed-derived phytoestrogens for palliation of the menopausal symptoms; therefore, this *in vitro* study was undertaken as a preliminary test of the combined effects of flaxseed and tamoxifen on estrogen-sensitive breast cancer. Human cancer cells were injected into the mammary fat pads of ovariectomized mice, and an estradiol (E2) pellet was implanted to stimulate tumor growth. [1]

After tumor growth occurred, the estradiol pellets were removed and the mice were divided into two groups. One group continued without estradiol stimulation of the cancer to mimic the post-menopausal patient; the other group had its estradiol pellet replaced to mimic pre-menopausal patients. Each group was further divided into subgroups receiving tamoxifen therapy, flaxseed alone, flaxseed and tamoxifen, and the positive and negative controls. Tumor area, proliferation and apoptotic indices were assessed. [1]

Interestingly, in the 'post-menopausal' mice without estradiol supplementation, the group receiving tamoxifen therapy showed an increase in tumor area over time compared to the negative control, which received no estradiol, tamoxifen, or flaxseed, leading the authors to postulate that tamoxifen was demonstrating an unexpected capacity for estrogenic stimulation. The increase was suppressed in the group treated with the combination of tamoxifen and flaxseed, suggesting that flaxseed may have anti-estrogenic properties. The flaxseed and tamoxifen group still had greater tumor weight and volume than the flaxseed alone, which had only slightly greater tumor weight and volume than no therapy at all. The apoptotic and proliferative indices of the tumors in the various groups showed similar patterns, with the negative control showing the lowest proliferation and highest apoptotic indices, while the flaxseed seemed to ameliorate a tamoxifen-induced increase in proliferation and decrease in apoptosis. Based on the comparison to negative controls, flaxseed did not exert a strong estrogenic effect on the tumors, an observation of clinical significance for flaxseed supplementation in breast cancer patients. [1]

In the 'pre-menopausal' mice with estradiol supplementation, flaxseed alone showed a lesser suppression of tumor weight and volume than tamoxifen, which itself had less an effect than observed in the flaxseed and tamoxifen group. Similarly, flaxseed in combination showed a greater reduction in proliferation and a greater increase in apoptosis of tumor cells than either flaxseed or tamoxifen alone. [1]

The authors' conclusions seem well-founded in light of their results, namely, that the flaxseed-derived lignans appear to exert anti-proliferative and proapoptotic effects, as well as some effect on the hormonal milieu. Further, the *in vitro* evidence seems to suggest that observational studies should be conducted in humans to examine

combination tamoxifen and flaxseed therapy, as a synergistic effect was seen in the mouse animal model.

Demark-Wahnefried *et al* conducted an experiment in dietary flaxseed supplementation and its effects on prostate carcinoma in a transgenic mouse model of adenocarcinoma of the mouse prostate. At 30 weeks the flaxseed-treated mice had significantly fewer aggressive tumors than the controls, as well as significantly lower levels of proliferation and higher levels of apoptosis in the prostatic tissue. [11]

Flaxseed in humans

Demark-Wahnefried *et al* also carried out two pilot studies in male patients with prostate cancer to examine the effects of flaxseed supplementation on prostate cancer and dysplasia. [5,6] In the first study, they selected a cohort of 25 patients anticipating radical prostatectomy to be put on a low-fat diet (20% of total kcal) with roughly 3 tablespoons of flaxseed per day. Significant decreases in total serum testosterone, free androgen index, and total cholesterol were detected in diet-treated patients over the course of three weeks, however, the study did not indicate levels in the control group. [5] Without direct comparison to control, it is not possible to determine causality in the experimental group. Additionally, the low-fat diet confounds the data with respect to the specific effects of flaxseed.

In the second pilot study, fifteen patients who had had a prostate biopsy indicating prostatic intraepithelial dysplasia (PIN) and/or atypia and were scheduled to undergo repeat biopsy were put on a low-fat (less than 20% of total kcal), flaxseed-supplemented (30g/day) diet in the interim. These results showed significant declines in PSA but not in the total testosterone or cholesterol. Biopsy comparisons showed no significant changes, and the reference pathologist who made the initial diagnosis of PIN reversed diagnosis during a blinded review of almost half the biopsies. [6] Taken together, the two studies do not generate an optimistic picture of dietary flaxseed supplementation in prostate cancer, with inconsistent results in two fairly similar trials.

In a third retrospective study, 144 women newly diagnosed with breast cancer were compared to age- and residence-matched controls selected at random from electoral rolls. The women collected three consecutive 24-h urinary samples, and the samples were assayed for phytoestrogen levels, including enterolactone and enterodiol levels. Of the phytoestrogens tested, enterolactone showed a three-fold breast cancer risk reduction for the highest quartile compared to the lowest quartile of secretion levels in patient urine. Problems with the study design include the wide age-range in the cohort (30-63 years old). Given the results of the estrogen-sensitive animal models, it may be important to divide study groups into pre- and post-menopausal cohorts to render the hormonal milieu homogenous. Nevertheless, this is an excellent preliminary retrospective analysis of statistical risk for breast cancer. [8]

The data on possible antitumorigenic effects of flaxseed in humans are inconclusive at best. The *in vitro* data are provoking and SDG as an anticarcinogenic agent warrants further study. Its potential mechanism of action in cancer prevention remains unclear, but the current animal studies seem to suggest that its estrogenic/antiestrogenic effects, as well as some apoptotic and antiproliferative effects, may play a role. Human breast cancer seems a logical clinical framework for further research, and the risk analysis study cited above constitutes only very preliminary data.

Flaxseed supplementation for its own sake seems harmless, however, and though this review did not address its other potentially beneficial health effects, its high fiber content and omega-3 fatty acids are thought to have positive effects on patients' cardiovascular disease profile.

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