

Cancer Research References

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ABSTRACTS and SUMMARIES

1. Since lignans have been suggested to have some cancer-protective effects, flaxseed, the most abundant source of lignan precursors, was tested for its effect on early markers of risk for mammary carcinogenesis. Supplementation of a high-fat diet with flaxseed flour (FF) or defatted flaxseed meal (FM) (5% or 10%) reduced the epithelial cell proliferation by 38.8-55.4% and nuclear aberrations by 58.8-65.9% in female rat mammary gland, with optimum effects seen with the 5% FF. These protective effects were accompanied by increases in urinary lignan excretion indicating that they may be related to the ability of flaxseed to provide lignan precursors. (Serraino M & Thompson L, Cancer Lett, 60:135, 1991)

2. Flaxseed ingestion produces potentially anticarcinogenic lignans in the colon. This study determined that flaxseed decreases the risk for colon carcinogenesis. In the descending colon of supplemented groups, the total number of aberrant crypts and foci were significantly reduced by 41-53% and 48-57%, respectively. Flaxseed may reduce the risk for colon carcinogenesis. (Serraino M & Thompson L, Cancer Lett, 63:159, 1992)

3. Flaxseed lignans have antitumor, antimitotic, antioxidant and weak estrogenic activities, are potentially the richest source of phytoestrogens in the human diet and may be linked to a low incidence of breast and colon cancer. Secoisolariciresinol was discovered to be a very potent antioxidant similar to BHA. No toxicity was found in the lignans. (Obermeyer W, et al (US Food and Drug Administration, Center for Food Safety and Applied Nutrition, Div. Contaminants Chem., Natural Products Branch), Meeting Of The Federation Of American Societies For Experimental Biology On Experimental Biology March/April, 1993, FASEB J (Fed Am Soc Exp Biol), A863, 1993)

4. Flaxseed SDG may have a therapeutic role in lupus nephritis. (Clark W, et al Lupus, 9(6): 429, 2000)

5. Dietary estrogens, such as lignan-rich flaxseed, are similar in structure to endogenous sex steroid hormones and act in vivo to alter hormone metabolism and reduce subsequent cancer risk in postmenopausal women. (Hutchins A, Cancer Epidemiol Biomarkers Prev, 9(10): 1113, 2000)

6. Asian men have much lower incidences of prostate cancer and possibly of benign prostatic hyperplasia (BPH) than their Western counterparts. Vegetarian men also have a lower incidence of prostate cancer than omnivorous males. Plant lignans give rise to the mammalian lignans, enterodiol and enterolactone; the richest source is linseed (flaxseed). In addition to their oestrogenic activity, these plant compounds can interfere with steroid metabolism and bioavailability, and also inhibit enzymes, such as tyrosine kinase and topoisomerase, which are

crucial to cellular proliferation and hence may contribute to lower incidences of prostate cancer. (Eur Urol, 35(5-6): 377, 1999)

7. Flaxseed ingestion produces large amounts of mammalian lignans with weak estrogenic/anti-estrogenic properties reduced adult relative prostate weight and cell proliferation, suggesting potential protection against prostatic disease, without affecting sex hormone levels. (Tou J, et al, J Toxicol Environ Health, 56(8): 555, 1999)

8. SDG is a plant lignan isolated from flaxseed. Lignans are platelet-activating factor-receptor antagonists that inhibit the production of oxygen radicals by polymorphonuclear leukocytes. SDG is an antioxidant. Antioxidants studied thus far are known to reduce hypercholesterolemic atherosclerosis. Research suggests that SDG reduces hypercholesterolemic atherosclerosis and that this effect is associated with a decrease in serum cholesterol, LDL-C, and lipid peroxidation product and an increase in HDL-C and antioxidant reserve. (Prasad K, Circulation, 99(10): 1355, 1999)

9. Phytoestrogens are diphenolic compounds that are present in several plants eaten by human beings. Flaxseed is a particularly abundant source of phytoestrogens. When ingested in relatively large amounts, phytoestrogens have been shown to have significant estrogen agonists/antagonists effects in animals and humans. There is epidemiological, laboratory and clinical evidence which indicates that phytoestrogens, like certain selective estrogen receptor modulators, have an antiproliferative effect on the breast, and positive effects on the lipoprotein profile and bone density. They might also improve some of the climacteric symptoms. (Brzezinski A & Debi A, Eur J Obstet Gynecol Reprod Biol, 85(1): 47, 1999)

10. The antioxidant activities of the flaxseed lignan secoisolariciresinol diglycoside (SDG) and its mammalian lignan metabolites, enterodiol (ED) and enterolactone (EL), were evaluated in both lipid and aqueous in vitro model systems. All three lignans significantly ($p < \text{or} = 0.05$) inhibited the linoleic acid peroxidation at both 10 and 100 microM over a 24-48 h of incubation at 40 degrees C. The efficacy of SDG and particularly the mammalian lignans ED and EL to act as antioxidants in lipid and aqueous in vitro model systems, at relatively low concentrations (i.e. 100 microM), potentially achievable in vivo, is an evidence of a potential anticarcinogenic mechanism of flaxseed lignan SDG and its mammalian metabolites ED and EL. (Kitts D, et al, Mol Cell Biochem, 202(1-2): 91, 1999)

11. Flaxseed, the richest known source of plant lignans, has been shown to have chemo-protective effects in animal and cell studies. Some of its effects may be mediated through its influence on endogenous hormone production and metabolism. Flaxseed supplementation significantly increased urinary 2-OHEstrogen excretion ($p < 0.0005$) and the urinary 2/16 alpha-OHE1 ratio ($p <$

0.05) in a linear, dose-response fashion. These results suggest that flaxseed may have chemo-protective effects in postmenopausal women. (Haggans C, et al, Nutr Cancer, 33(2): 188, 1999)

12. Flaxseed is high in secoisolariciresinol diglycoside (SDG), the precursor of mammalian lignans, which can affect mammary gland structures. Lifetime or gestation and lactation exposure to 5 or 10% flaxseed induce structural changes in the mammary gland that may potentially reduce mammary cancer risk. (Tou J & Thompson L, Carcinogenesis, 20(9): 1831, 1999)

13. Flaxseed and SDG, regardless of dose, appeared to delay the progression of MNU-induced mammary tumorigenesis. (Rickard S, et al, Nutr Cancer; 35(1): 50, 1999)

14. Dietary supplementation with flaxseed or its lignan SDG has reduced induced mammary tumor size and number in rats. There was a dose-dependent effect of SDG on tumor multiplicity, lowest in the HSDG group (high SDG 5%) and highest in the LSDG (low SDG 2.5%) group throughout treatment, indicating that HSDG inhibited, whereas LSDG promoted, MNU-induced mammary tumor development. Tumor invasiveness and grade were decreased in all treatment groups compared with the BD (basal diet). Flaxseed and SDG treatment, regardless of dose, appeared to delay the progression of MNU-induced mammary tumorigenesis. (Rickard S, et al, Nutr Cancer; 35(1): 50, 1999)

15. Because flaxseed and its lignans are colon cancer protective, it is concluded that, in contrast to other studies, beta-glucuronidase activity may play a beneficial role in their presence by increasing mammalian lignan absorption and enterohepatic circulation. (Jenab M, et al, Nutr Cancer, 33(2): 154, 1999)

16. Flax seed is the richest source of omega-3 fatty acid and lignans. Omega-3 Fatty acid suppresses the production of interleukin-1 (IL-1), tumor necrosis factor (TNF) and leukotriene B4 (LTB4), and of OFRs by polymorphonuclear leukocytes (PMNLs) and monocytes. Lignans possess anti-platelet activating factor (PAF) activity and are antioxidant. PAF, IL-1, TNF and LTB4 are known to stimulate PMNLs to produce OFRs. Flaxseed would, therefore, reduce the levels of OFRs and hence would prevent the development of hypercholesterolemic atherosclerosis. In rabbits, flax seed reduced the development of aortic atherosclerosis by 46% and reduced the PMNL-CL without significantly lowering the serum cholesterol. Flax seed in normocholesterolemic rabbits increased serum total cholesterol and decreased PMNL-CL without significantly affecting the serum TG. Modest dietary flax seed supplementation is effective in reducing hypercholesterolemic atherosclerosis markedly without lowering serum cholesterol. Its effectiveness against hypercholesterolemic atherosclerosis could be due to suppression of enhanced production of OFRs by PMNLs in hypercholesterolemia. Dietary flax seed supplementation could, therefore,

prevent hypercholesterolemia-related heart attack and strokes. (Ogborn M, et al, Kidney Int 55(2): 417, 1999)

17. Dietary supplementation with secoisolariciresinol diglycoside (SDG), a lignan precursor isolated from flaxseed, significantly reduced pulmonary metastasis of melanoma cells and inhibited the growth of metastatic tumors that formed in the lungs. (Li D, et al, Cancer Lett, 142(1): 91, 1999)

18. Flaxseed, the richest source of lignans reduces metastasis and inhibits the growth of the metastatic secondary tumors in animals. Flaxseed may be a useful nutritional adjuvant to prevent melanoma metastasis in cancer patients. (Yan L, et al, Cancer Lett, 124(2): 181, 1998)

19. Flaxseed contains lignans that have antioxidant activities and inhibit platelet-activating factor (PAF). Pretreatment with flaxseed attenuated endotoxin induced cardiac dysfunction and cellular damage. Flaxseed antioxidant and anti-PAF agents may be effective in the treatment of ET shock. (Pattanaik U & Prasad K, J Cardiovasc Pharmacol Ther, 3(4): 305, 1998)

20. The mammalian lignans enterolactone (EL) and enterodiol (ED) derived from precursors in foods, particularly flaxseed, have been shown to reduce the mammary tumor growth due to their antiestrogenic properties. Lignans are growth inhibitors of colon tumor cells and they may act through mechanism(s) other than antiestrogenic activity. (Sung M, et al, Anticancer Res 18(3A): 1405, 1998)

21. Flax seed is the richest source of omega-3 fatty acid and lignans. Omega-3 fatty acid suppresses the production of interleukin-1 (IL-1), tumor necrosis factor (TNF) and leukotriene B4 (LTB4), and of OFRs by polymorphonuclear leukocytes (PMNLs) and monocytes. Lignans possess anti-platelet activating factor (PAF) activity and are antioxidant. PAF, IL-1, TNF and LTB4 are known to stimulate PMNLs to produce OFRs. Flaxseed would, therefore, reduce the levels of OFRs and hence would prevent the development of hypercholesterolemic atherosclerosis. Flax seed reduced the development of aortic atherosclerosis by 46% and reduced the PMNL-CL without significantly lowering the serum cholesterol. Modest dietary flax seed supplementation is effective in reducing hypercholesterolemic atherosclerosis markedly without lowering serum cholesterol. Dietary flax seed supplementation could, therefore, prevent hypercholesterolemia-related heart attack and strokes. (Prasad K, Atherosclerosis, 132(1): 69, 1997)

22. Flaxseed, the richest source of mammalian lignan precursors, such as secoisolariciresinol diglycoside (SD), has been shown over the short term to decrease some early markers of colon cancer risk. This study determined that flaxseed has a colon cancer protective effect, that it is due, in part, to SD and that

the protective effect of flaxseed is associated with increased beta-glucuronidase activity. (Jenab M & Thompson L, Carcinogenesis, 17:1343, 1996)

23. Secoisolariciresinol diglucoiside (SDG), an antioxidant in flaxseed, is metabolized in the body and these metabolites have antioxidant activity which are even more potent than SDG. The effectiveness of SDG in hypercholesterolemic atherosclerosis, diabetes, and endotoxic shock could be due to these metabolites. (Prasad K, Int. J. Angiol, 9(4): 220, 2000)

24. Secoisolariciresinol diglycoiside (SD), a mammalian lignan precursor found in flaxseed and tested for effects on mammary tumorigenesis, resulted in a 37% reduction ($p < 0.05$) in the number of tumors per tumor-bearing rat and a 46% reduction ($p < 0.05$) in the number of tumors per number of rats in each group. This study showed, for the first time, that SD has an antitumor effect when provided at the early promotion stage of tumorigenesis. (Thompson L, et al, Nutr Cancer, 26:159, 1996)

25. Flaxseed 18-3 (n-3) alpha-linoleic acid showed a marked immunomodulatory effect on the exhaustive exercise-related immunosuppression, as compared to the effects of other PUFA. (Benquet C, et al, J Toxicol Environ Health, 43: 225, 1994)

26. Reactive oxygen species (ROS) have been implicated in the development of diabetes mellitus. SDG isolated from flaxseed is an antioxidant. An investigation was made of the effects of SDG on the development of diabetes in rat, to determine if SDG can prevent/reduce the development of diabetes and if this prevention/reduction is associated with reduction in oxidative stress. RESULTS: SDG prevented the development of diabetes by 75%. (Prasad K, et a, Mol Cell Biochem, 206(1-2): 141, 2000; Prasad K, Mol Cell Biochem, 209(1-2): 89, 2000)

27. Flaxseed and its lignan secoisolariciresinol diglycoiside (SDG) inhibit mammary tumor development in rats. Increased plasma insulin-like growth factor I (IGF-I) concentrations are associated with increased breast cancer risk. The anticancer effect of flaxseed and SDG may be related, in part, to reductions in plasma IGF-I. (Rickard S, et al, Cancer Lett, 8: 161(1): 47, 2000)

28. Vitamin E-deficient diets containing 5 to 20% ground flaxseed protected mice against the malarial parasite Plasmodium voelii as shown by decreased parasitemia and enhanced survival. (Levander O, et al, (USDA/ARS Human Nutrition Research Center, Vitamin Mineral Nutrition Laboratory), Nutrition Research, 11, 1991)

29. Flaxseed, a rich source of mammalian lignan precursor secoisolariciresinol-diglycoiside (SD) and alpha-linolenic acid (ALA), has been shown to be protective at the early promotion stage of carcinogenesis. In conclusion, the SD lignans in flaxseed appears to be beneficial throughout the promotional phase of

carcinogenesis whereas the oil component is more effective at the stage when tumors have already been established. (Thompson L, et al, Carcinogenesis, 17:1373, 1996)

30. Clinical Trial with Prostate Cancer Patients. Dietary fat and fiber affect hormonal levels and may influence cancer progression. Flaxseed is a rich source of lignan and omega-3 fatty acids and may thwart prostate cancer. The potential effects of flaxseed may be enhanced with concomitant fat restriction. We undertook a pilot study to explore whether a flaxseed-supplemented, fat-restricted diet could affect the biomarkers of prostatic neoplasia.

CONCLUSIONS: These pilot data suggest that a flaxseed-supplemented, fat-restricted diet may affect prostate cancer biology and associated biomarkers. Further study is needed to determine the benefit of this dietary regimen as either a complementary or preventive therapy.

(Denmark-Wahnefried W, et al. Urology. 58:47-52, 2001.)

31. The Phipps Study. Abstract. Lignans are a group of phytochemicals shown to have weakly estrogenic and antiestrogenic properties. Two specific lignans, enterodiol and enterolactone, are absorbed after formation in the intestinal tract from plant precursors particularly abundant in fiber-rich food and are excreted in the urine. We evaluated the effect of the ingestion of flax seed powder, known to produce high concentrations of urinary lignans, on the menstrual cycle in 18 normally cycling women, using a balanced randomized cross-over design. Each subject consumed her usual omnivorous, low fiber (control) diet for 3 cycles and her usual diet supplemented with flax seed for another 3 cycles. The second and third flax cycles were compared to the second and third control cycles. Three anovulatory cycles occurred during the 36 control cycles, compared to none during the 36 flax seed cycles. Compared to the ovulatory control cycles, the ovulatory flax cycles were consistently associated with longer luteal phase (lp) lengths (mean +/- sem, 12.6 +/- 0.4 Vs. 11.4 +/- 0.4 Days; p = 0.002). There were no significant differences between flax and control cycles for concentrations of either estradiol or estrone during the early follicular phase, midfollicular phase, or lp. Although flax seed ingestion had no significant effect on lp progesterone concentrations, the lp progesterone/estradiol ratios were significantly higher during the flax cycles. Midfollicular phase testosterone concentrations were slightly higher during flax cycles. Flax seed ingestion had no effect on early follicular phase concentrations of dhea-s, prl, or sex hormone-binding globulin. Our data suggest a significant specific role for lignans in the relationship between diet and sex steroid action, and possibly between diet and the risk of breast and other hormonally dependent cancers. (Phipps W, et al, J Clinl Endocrinol Metab, 77(5), 1993)