



Appendix III:

MEDLINE and CAPLUS literature search on  
flaxseed lignans safety and toxicity

Research Topic task started on Tue Oct 25, 2005 at 9:07 AM

5 Research Topic candidates were identified in MEDLINE and CAPLUS

using the phrase "flaxseed and lignan"

Selected 2 of 5 candidate topics.

48 references were found containing "flaxseed and lignan" as entered.

330 references were found containing both of the concepts "flaxseed" and "lignan".

Research Topic Refine started

45 references were found when refined using the phrase "toxicity or safety or adverse effect"

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### Bibliographic Information

**Flaxseed oil and bone development in growing male and female mice.** Cohen Stacey L; Ward Wendy E Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada Journal of toxicology and environmental health. Part A (2005), 68(21), 1861-70. Journal code: 100960995. ISSN:1528-7394. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16207634 AN 2005532848 In-process for MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### Abstract

Flaxseed is being increasingly incorporated into foods as a result of its proposed health benefits. Combined with the fact that bone is sensitive to dietary changes in fatty acids, the optimization of bone metabolism during childhood may be influenced by altering the type and amounts of fatty acids consumed. The effects of whole flaxseed or its purified lignan on bone development have been investigated, but positive and/or negative effects of flaxseed oil (FO), rich in alpha-linolenic acid (ALA), on bone development have not been reported. The objective of this study was to

elucidate the effects of a 10% FO diet on indices of bone health, including bone mass and biomechanical bone strength. Male and female mice were fed either a 10% flaxseed oil (FO) or a 10% corn oil (CO) diet from postnatal day (PND) 28 until PND 91. Male and female mice fed FO converted ALA to eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) as indicated by significantly higher serum EPA and DHA; however, serum cytokines (interleukin-1beta, interleukin-6, tumor necrosis factor-alpha) with the potential to modulate bone metabolism did not significantly differ among groups. As expected, serum linoleic acid and arachidonic acid were significantly lower among mice fed FO. Feeding FO diet did not result in a higher or lower bone mass or stronger or weaker femurs and lumbar vertebra than in mice fed CO diet in either gender, suggesting that the level of ALA attainable in a 10% flaxseed oil diet is safe with regard to bone development in growing mice.

### **Bibliographic Information**

**Enterolactone induces apoptosis and inhibits growth of Colo 201 human colon cancer cells both in vitro and in vivo.** Danbara Naoyuki; Yuri Takashi; Tsujita-Kyutoku Miki; Tsukamoto Reiko; Uehara Norihisa; Tsubura Airo Department of Pathology II, Kansai Medical University, Moriguchi, Osaka 570-8506, Japan Anticancer research (2005), 25(3B), 2269-76. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16158974 AN 2005488549 In-process for MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

**BACKGROUND:** The mammalian lignan enterolactone (ENL) is produced from plant lignans which are present in large amounts in flaxseed (linseed). The effect of ENL on colon cancer cell growth in vitro and in vivo, and its mechanisms of action, have not been studied in detail. **MATERIALS AND METHODS:** The growth of the colo 201 human colon cancer cell line was examined by colorimetric 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium (MTS) assay, while the expression of apoptosis- and proliferation-related proteins (p53, Bax, Bcl-xL and S, Bcl-2, Caspase-8, Caspase-3 and proliferating cell nuclear antigen (PCNA)) were examined by Western blotting. In vivo tumor growth was examined by transplanting colo 201 cells into ENL-treated and placebo-treated athymic mice. **RESULTS:** The MTS assay showed that ENL suppressed colo 201 cell growth (IC<sub>50</sub> for 72 h: 118.4 microM) in vitro. On flow cytometry, induction of apoptosis was confirmed by the appearance of subG1 populations, while cell cycle progression was not affected. The expression of an apoptosis-suppressing protein (Bcl-2) was down-regulated, an apoptosis-enhancing protein (cleaved form of Caspase-3) was up-regulated, proliferation-related PCNA protein was down-regulated and p53, Bax, Bcl-xL and S and Caspase-8 levels were unchanged. ENL, at a dose of 10 mg/kg given 3 times per week by subcutaneous injection, significantly inhibited the growth of colo 201 cells transplanted into athymic mice without any adverse effects. **CONCLUSION:** ENL suppressed colo 201 human colon cancer cell growth both in vitro and in vivo. The tumor-suppressing mechanisms included apoptosis and decreased cell proliferation.

### **Bibliographic Information**

**Effect of chronic administration of lignan complex isolated from flaxseed on the hemopoietic system.** Prasad Kailash Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, Canada. prasadk@usask.ca Molecular and cellular biochemistry (2005), 270(1-2), 139-45. Journal code: 0364456. ISSN:0300-8177. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15792363 AN 2005159727 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

Lignan complex has been isolated from flaxseed. It has been shown to reduce serum lipids and the

extent of hypercholesterolemic atherosclerosis. However, it is not known whether the chronic use of lignan complex has any adverse effects on the hemopoietic system. The effects of lignan complex (40 mg/kg body wt orally daily for 2 months) on the red blood cells (RBC) count, mean corpuscular volume (MCV), red cell distribution width (RDW), hematocrit (Hct), hemoglobin (Hb), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and counts of white blood cell (WBC), granulocytes, lymphocytes, monocytes and platelet, and platelet volume were investigated in normo- and hypercholesterolemic rabbits. The results show that lignan complex had no adverse effects of counts of RBC, WBC, granulocytes, lymphocytes, monocytes and platelet in both the normo- and hyper-cholesterolemic rabbits. The values for MCV, RDW, Hct, Hb, MCH, MCHC, and platelet volume were similar in lignan complex-treated or untreated normo- and hypercholesterolemic rabbits. It is concluded that chronic use of lignan complex had no adverse effects on the hemopoietic system.

### **Bibliographic Information**

**Health effects of phytoestrogens.** Branca Francesco; Lorenzetti Stefano National Institute for Research on Food and Nutrition, Rome, Italy. f.branca@agora.it Forum Nutr (2005), (57), 100-11. Journal code: 101194770. ISSN:1660-0347. Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW) written in English. PubMed ID 15702593 AN 2005073643 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

Phytoestrogens are naturally occurring plant-derived phytochemicals, whose common biological roles are to protect plants from stress or to act as part of a plant's defense mechanism. Although composed of a wide group of nonsteroidal compounds of diverse structure, phytoestrogens have been shown to bind estrogen receptors and to behave as weak agonist/antagonist in both animals and humans. Phytoestrogens include mainly isoflavones (IF), coumestans, and lignans. These compounds are known to be present in fruits, vegetables, and whole grains commonly consumed by humans. IF are found in legumes--mainly soybeans--whereas flaxseed is a major source of lignans, and coumestans are significantly present in clover, alfalfa and soybean sprouts. 8-Prenyl flavonoids are common in vegetables. Bioavailability of IF requires an initial hydrolysis of the sugar moiety by intestinal beta-glucosidases to allow the following uptake by enterocytes and the flow through the peripheral circulation. Following absorption, IF are then re-conjugated mainly to glucuronic acid and to a lesser degree to sulphuric acid. Gut metabolism seems key to the determination of the potency of action. Several epidemiological studies correlated high dose consumptions of soy IF with multiple beneficial effects on breast and prostate cancers, menopausal symptoms, osteoporosis, atherosclerosis and stroke, and neurodegeneration. For the relief of menopausal symptoms a consumption of 60 mg aglycones/day has been suggested; for cancer prevention a consumption between 50 and 110 mg aglycones/day is considered beneficial to reduce risks of breast, colon and prostate cancer; to decrease cardiovascular risk a minimum intake of 40-60 mg aglycones/day, together with about 25 g of soy protein has been suggested. For improvement in bone mineral density, 60-100 mg aglycones/day for a period of at least 6-12 months could be beneficial.

### **Bibliographic Information**

**A thirteen week dietary toxicity study with 7-hydroxymatairesinol potassium acetate (HMRLignan) in rats.** Lina B; Korte H; Nyman L; Unkila M TNO Nutrition and Food Research, Department of Toxicology and Applied Pharmacology, Zeist, The Netherlands Regulatory toxicology and pharmacology : RTP (2005), 41(1), 28-38. Journal code: 8214983. ISSN:0273-2300. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15649825 AN 2005024205 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

Plant lignan 7-hydroxymatairesinol (7-HMR) is a novel precursor of the mammalian lignan enterolactone. A 13 week toxicity study at dietary levels of 0, 0.25, 1, and 4% (w/w) of potassium acetate complex of 7-HMR (HMRlignan) was conducted in the Wistar rat. These dietary levels resulted in an average daily intake of 160, 640, and 2600 mg HMRlignan/kg body weight/day, respectively. A considerable systemic exposure of HMRlignan was verified by dose-related increases in plasma total (conjugated and unconjugated) concentration of 7-HMR and metabolites enterolactone, 7-hydroxyenterolactone, and matairesinol. Enterolactone appeared to be the major metabolite. Most (>96%) of the circulating 7-HMR and enterolactone was in conjugated form as measured from the low-dose rat plasma samples. HMRlignan exposure did not significantly affect clinical signs, ophthalmoscopy or neurobehavioural observations, and motor activity. Transient reductions in food intake and body weight gain in the mid- and high-dose group were ascribed to decreased palatability of the test feed. Only in males of the high-dose group the body weights remained slightly reduced throughout the study. In the high-dose group the number of thrombocytes (females), and total white blood cell count (males) were increased. Plasma triglycerides were dose-dependently depressed in males of all test groups and in females of the mid- and high-dose group, while plasma total cholesterol, and phospholipids were decreased in high-dose males. These changes, which have also been reported for other (flaxseed) lignans, were not considered to represent adverse effects. The relative weight of the kidneys was increased in males of the high-dose group. The weight of the full and empty caecum showed dose-related increases in males of all treatment groups and in females of the high-dose group. Absolute ovary weights were decreased in all treatment groups while decreases in relative ovary weights were confined to the mid- and high-dose group.

In addition, a marginal lengthening of the estrus cycle was noted in high-dose females. Apart from prevention of hyaline droplet nephropathy in all high-dose male rats, there were no treatment-related histopathological alterations. It was concluded that HMRlignan showed weak antiestrogen-like activity which may be mediated through enterolactone metabolite. Based on declined ovary weight, the no observed adverse effect level of HMRlignan was set at 0.25% in feed corresponding to 160 mg/kg body weight/day.

### **Bibliographic Information**

**The effects of dietary flaxseed on the Fischer 344 rat: II. Liver gamma-glutamyltranspeptidase activity.** Hemmings Susan J; Westcott Neil; Muir Alister; Czechowicz Dominika Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada. [hemmings@sask.usask.ca](mailto:hemmings@sask.usask.ca) Cell biochemistry and function (2004), 22(4), 225-31. Journal code: 8305874. ISSN:0263-6484. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15248182 AN 2004342805 In-process for MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

The effect of 10% flax chow consumption from the 30th to the 130th day after birth was examined in male Fischer 344 rats. The effects of both the high lignan/high oil Norlin strain and a high lignan/low oil Solin strain of flaxseed were compared. Physically and behaviourally there were no differences in rats belonging to the three dietary groups at any time. At 50 and 100 days of dietary exposure, blood glucose levels were the same in Norlin and Solin flax chow-fed and as well as regular chow-fed rats; there were no signs of toxicity in the Norlin and Solin flax-fed rats since their plasma levels of alanine aminotransferase were the same and equal to those of regular chow-fed rats. The activity of gamma-glutamyltranspeptidase (gammaGT) displayed an increase in the liver homogenates of flax chow-fed rats. This increase was the same in Norlin and Solin flax-fed rats at 50 and 100 days. Thus the liver effect was not oil, but lignan, likely secoisolariciresinol diglucoside (SDG), induced and was effected early on, and sustained, after flax exposure. The degree of heat activation of liver homogenate gammaGT was the same in regular chow-fed and flax chow-fed rats. Compared to liver homogenate gammaGT activity, the soluble form of gammaGT was expressed at very low levels while the plasma membrane-bound form of gammaGT was expressed at very high

levels in rat liver in both regular chow-fed and flax chow-fed rats. There was no effect of flax feeding on the soluble form of liver gammaGT which was expressed at a very low level. Flax feeding effected an increase in the activity of gammaGT in isolated plasma membrane fractions which mirrored that in liver homogenates: the same degree of increase was seen in Noriin flax chow-fed and Solin flax chow-fed rats. Flax consumption effects an increase in the activity of liver gammaGT at the level of the plasma membrane which is lignan dependent, physiologically relevant and may be linked to hepatoprotection against injury through an increase in reduced glutathione. Copyright 2004 John Wiley & Sons, Ltd.

### **Bibliographic Information**

**The effects of dietary flaxseed on the Fischer 344 rat: I. Development, behaviour, toxicity and the activity of liver gamma-glutamyltranspeptidase.** Hemmings Susan J; Barker Lorraine Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada. hemmings@sask.usask.ca Cell biochemistry and function (2004), 22(2), 113-21. Journal code: 8305874. ISSN:0263-6484. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15027100 AN 2004133541 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

The effect of exposure to, followed by consumption of, 10% flax chow from the 18th day of gestation to the 86th day after birth was examined in male and female Fischer 344 rats. Growth curves of the flax chow-fed rats were identical to those of regular chow-fed rats, as were such developmental milestones as pinna development, growth of hair and eye opening. Acoustical startle and the righting reflexes, developmental behavioural indices, were also the same. Blood glucose levels were comparable in flax chow-fed and regular chow-fed rats at all stages of development, indicating that flax is without effect on glucose balance. There were no signs of toxicity in the flax chow-fed rats since their plasma levels of alanine aminotransferase and gamma-glutamyltranspeptidase (gammaGT) were the same as those of regular chow-fed rats. The activity of gammaGT displayed an increase in the livers of flax chow-fed rats after puberty, more so in the male-four-fold-than in the female-1.38-fold. This is suggestive of an estrogenic effect which implicates an effect of an estrogenic flax lignan. An hepatobeneficial effect of the flax-induced increase in liver gammaGT is discussed. In summary, dietary 10% flax chow is without long-term effect on growth, development and behaviour, is non-toxic and may be hepatoprotective. Copyright 2003 John Wiley & Sons, Ltd.

### **Bibliographic Information**

**Flax facts. A grain for good health.** Campbell Amy P Office of Disease Management, Joslin Diabetes Center, Boston, Massachusetts, USA Diabetes self-management (2003), 20(6), 18, 20-2. Journal code: 9883682. ISSN:0741-6253. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 14971334 AN 2004081582 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Bibliographic Information**

**Flaxseed oil: healthful or harmful for men?** Anonymous Harvard men's health watch (2003), 8(2), 5-6, 8. Journal code: 9802701. ISSN:1089-1102. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 14505958 AN 2003528197 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Bibliographic Information**

**Exposure to flaxseed or its purified lignan during suckling inhibits chemically induced rat mammary tumorigenesis.** Chen Jianmin; Tan Kah Poh; Ward Wendy E; Thompson Lilian U

Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario M5S 3E2, Canada Experimental biology and medicine (Maywood, N.J.) (2003), 228(8), 951-8. Journal code: 100973463. ISSN:1535-3702. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 12968067 AN 2003427256 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### Abstract

Previous studies have shown that feeding flaxseed (FS) or its lignan secoisolariciresinol diglucoside (SDG) to rat dams during lactation enhances the differentiation of rat mammary gland in the female offspring. This study determined whether exposure to a diet with 10% FS or SDG (equivalent to the amount in 10% FS) during suckling could protect against 9,10-dimethyl-1,2-benzanthracene (DMBA)-induced rat mammary tumorigenesis later in life. Dams were fed the AIN-93G basal diet (BD) throughout pregnancy. After delivery, dams were randomized to continue on BD or were fed BD supplemented with 10% FS or SDG during lactation. Three-day urine of dams was analyzed for mammalian lignans. After weaning, all offspring were fed BD. At postnatal Days 49 to 51, during proestrus phase, offspring were gavaged with 5 mg of DMBA. At Week 21 post-DMBA administration, compared with the BD group, the FS and SDG groups had significantly lower ( $P < 0.05$ ) tumor incidence (31.3% and 42.0% lower, respectively), total tumor load (50.8% and 62.5% lower, respectively), mean tumor size (43.9% and 67.7% lower, respectively), and tumor number (46.9% and 44.8% lower, respectively) per rat. There was a significant decreasing trend ( $P < 0.05$ ) in final tumor weights in rats fed FS or SDG. The high urinary lignan excretion in dams fed with FS or SDG corresponded with the reduced tumor development. The FS and SDG groups did not differ significantly in tumor indices, indicating that the effect of FS is primarily due to its SDG. There were no significant changes in selective reproductive indices measured among dams and offspring. In conclusion, exposure to FS or SDG during suckling suppressed DMBA-induced rat mammary tumorigenesis, suggesting that exposure to lignans at this early stage of mammary gland development reduces susceptibility to mammary carcinogenesis later in life without adverse effects on selective reproductive indices in dams or offspring.

### Bibliographic Information

**Exposure to flaxseed or its purified lignan during suckling only or continuously does not alter reproductive indices in male and female offspring.** Ward W E; Chen J; Thompson L U Department of Nutritional Sciences, University of Toronto, Ontario, Canada Journal of toxicology and environmental health. Part A (2001), 64(7), 567-77. Journal code: 100960995. ISSN:1528-7394. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11760154 AN 2002035689 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### Abstract

Based on the reported health benefits of flaxseed, many Canadians are choosing to consume flaxseed or flaxseed-containing foods. However, the safety of exposure to flaxseed during early life such as the suckling period has not been studied, despite the fact that components in flaxseed with potential hormone-like effects can be transferred to nursing offspring via mother's milk. Previous investigations demonstrated that maternal feeding of a 10% flaxseed diet during pregnancy and lactation resulted in estrogenic effects on reproductive indices among male and female offspring. These effects were attributed to the potential estrogenic activity of enterodiols and enterolactone, the two major mammalian lignans that are converted from secoisolariciresinol diglycoside (SDG) in flaxseed by colonic bacteria; however, the effect of exposure to purified SDG at the level of a 10% flaxseed diet was not studied. The objective of this study was to determine whether maternal feeding of flaxseed during lactation altered reproductive indices in male and female offspring. Rat dams were fed basal diet (BD) or BD containing either 100% flaxseed (10F) or the equivalent quantity of SDG present in the 10% (10S) flaxseed diet from the start of lactation until pups were 21

d old. At the end of lactation (postnatal day [PND] 21), suckling pups either continued on the mother's diet or were switched to BD until adolescence (PND 50) or young adulthood (PND 132) to determine if continuous exposure to flaxseed or SDG altered reproductive indices. The reproductive indices that were measured included anogenital distance from birth through PND 21, age and body weight at puberty onset (females only), estrous cycle length, reproductive organ weights at PND 50 and 132, and histological analysis of reproductive organs (uterus, ovaries, prostate) at PND 132.

There were no significant effects of exposing male or female offspring to flaxseed or SDG during suckling only or during suckling through the postsuckling period on any of the reproductive indices measured. These findings are in contrast to the estrogenic effects observed in male and female offspring exposed to flaxseed during fetal life through suckling and suggest that fetal life is a more hormone-sensitive period of development. Although maternal feeding of flaxseed during lactation appears to be safe with respect to reproductive indices among offspring, future investigation is required to elucidate whether there are any long-term implications with respect to fertility.

### **Bibliographic Information**

**Protective effects of dietary phytoestrogens in chronic renal disease.** Ranich T; Bhathena S J; Velasquez M T Division of Renal Diseases and Hypertension, Department of Medicine, George Washington University Medical Center, Washington, DC 20037, USA Journal of renal nutrition : official journal of the Council on Renal Nutrition of the National Kidney Foundation (2001), 11(4), 183-93. Journal code: 9112938. ISSN:1051-2276. Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW); (REVIEW, TUTORIAL) written in English. PubMed ID 11679998 AN 2001571569 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

Phytoestrogens are naturally occurring plant compounds that are present primarily in soybeans as isoflavones and in flaxseed as lignans. Because of their structural similarity to endogenous estrogens, phytoestrogens bind to both estrogen receptors (ER)-alpha and beta (but more strongly to ER-beta) and exert estrogen-like effects. There is increasing evidence that dietary phytoestrogens have a beneficial role in chronic renal disease. Nutritional intervention studies have shown that consumption of soy-based protein and flaxseed reduces proteinuria and attenuates renal functional or structural damage in animals and humans with various forms of chronic renal disease. It is not clear which component(s) of the soybean or flaxseed is (are) responsible for the protective effects observed in experimental animals and in limited studies in humans. Vegetable protein has been shown to have a beneficial effect on renal disease in animals and humans. Thus, the role of soy and flaxseed cannot be ruled out. Isoflavones and lignans are readily absorbed from the gut and converted to active metabolites, which may be partly responsible for the beneficial renal effects of soy protein and flaxseed. In addition, an interaction between type of protein and phytoestrogens is also possible. The biological actions of isoflavones and lignans have been well defined in different cell types in vitro and also in vivo, but how these compounds might reduce renal injury remains to be elucidated. Possible mechanisms include inhibition of cell growth and proliferation via ER-mediated mechanisms or non-ER-mediated pathways through inhibition of tyrosine protein kinases, modulation of growth factors involved in extracellular matrix synthesis and fibrogenesis, inhibition of cytokine-induced activation of transcription factors, inhibition of angiogenesis, antioxidative action, suppression of platelet activating factor and platelet aggregation, and immunomodulatory activity.

To date, clinical trials in humans are few, of relatively short duration, and involve a small number of patients. Prospective randomized trials are needed to evaluate the long-term safety and effectiveness of dietary phytoestrogens on renal disease progression in patients with chronic renal failure. Copyright 2001 by the National Kidney Foundation, Inc.

### **Bibliographic Information**

**The role of phytoestrogens in the prevention and treatment of osteoporosis in ovarian**

**hormone deficiency.** Arjmandi B H Department of Nutritional Sciences, Oklahoma State University, Stillwater 74078, USA. arjmand@okstate.edu Journal of the American College of Nutrition (2001), 20(5 Suppl), 398S-402S; discussion 417S-420S. Journal code: 8215879. ISSN:0731-5724. Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW); (REVIEW, TUTORIAL) written in English. PubMed ID 11603649 AN 2001557415 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

Ovarian hormone deficiency is a major risk factor for osteoporosis in postmenopausal women. Hormone replacement therapy (HRT) is perhaps the most effective treatment, as it has been demonstrated to both reduce the rate of bone loss and risk of fracture, including hip fracture. However, not all women who may benefit from HRT are willing to initiate this treatment due to fear of cancer and contraindications. Other therapeutic agents currently available are also associated with certain adverse effects. As a result, postmenopausal women are more inclined to use natural remedies to alleviate postmenopausal symptoms and help reduce their risk for chronic diseases such as osteoporosis. Recent reports support the notion that certain bioactive constituents, e.g., phytoestrogens, in plants play a role in maintaining or improving skeletal health. The main consumable plant sources of phytoestrogens include isoflavones and lignans found mainly in soybeans and flaxseed, respectively. Although this paper primarily focuses on the effects of soy protein or its isoflavones on bone, additional statements regarding the role of flaxseed and dried plums, a rich source of polyphenols, with respect to bone will be made.

#### **Bibliographic Information**

**Exposure to flaxseed and its purified lignan reduces bone strength in young but not older male rats.** Ward W E; Yuan Y V; Cheung A M; Thompson L U Department of Nutritional Sciences, University of Toronto, Ontario, Canada Journal of toxicology and environmental health. Part A (2001), 63(1), 53-65. Journal code: 100960995. ISSN:1528-7394. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11346133 AN 2001250385 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

Flaxseed is the richest source of the plant lignan secoisolariciresinol diglycoside (SDG), which is converted to the two major mammalian lignans, enterodiol (ED) and enterolactone (EL), by colonic bacteria. Because both ED and EL can produce biological effects similar to estrogen, exposure to lignans during early stages of development may adversely alter the normal development of bone in males since bone is a hormone-sensitive tissue. To determine whether early exposure to flaxseed or its lignan compromised the acquisition of bone mass or reduced bone strength, male offspring were exposed to one of three diets during lactation only (birth through postnatal day [PND] 21) via mother's milk or continuously from the start of lactation through to adolescence (PND 50) or young adulthood (PND 132). The diets were a basal diet (BD) that was devoid of phytoestrogens, BD containing 10% flaxseed, or BD containing the equivalent quantity of SDG present in a 10% flaxseed diet. To assess bone quantity, the bone mineral content (BMC) and bone mineral density (BMD) of femurs were assessed by dual-energy x-ray absorptiometry. Since the biomechanical properties of bone are indicators of the microarchitecture and thus bone quality, the biomechanical strength of femurs was assessed by three-point bending. At PND 50, ultimate bending stress and Young's modulus, measures of bone strength, were reduced among rats that received the 10% flaxseed diet from PND 0 through PND 50, while there were no marked differences in bone size, BMC, or BMD among groups. Interestingly, this effect does not appear to be due to the lignan in flaxseed, as continuous exposure to the diet containing the equivalent quantity of lignan (10 S diet) did not alter any measures of bone strength. In contrast to PND 50, bone strength did not differ among groups at PND 132, indicating that the compromise in bone strength was not sustained into early adulthood. Bone size, BMC, and BMD continued to be similar among treatment groups at PND 132.

In conclusion, exposing male rats to a diet containing 10% flaxseed or an equivalent quantity of lignan either during lactation only or through to early adulthood is safe with respect to bone health, as measures of bone mass and strength were similar to control rats.

### Bibliographic Information

**Comparative assessment of endocrine modulators with oestrogenic activity: I. Definition of a hygiene-based margin of safety (HBMOS) for xeno-oestrogens against the background of European developments.** Bolt H M; Janning P; Michna H; Degen G H Institut für Arbeitsphysiologie an der Universität Dortmund, Germany. bolt@arb-phys.uni-dortmund.de Archives of toxicology (2001), 74(11), 649-62. Journal code: 0417615. ISSN:0340-5761. Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW) written in English. PubMed ID 11218041 AN 2001203898 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### Abstract

A novel concept - the hygiene-based margin of safety (HBMOS) - is suggested for the assessment of the impact of potential endocrine modulators. It integrates exposure scenarios and potency data for industrial chemicals and naturally occurring dietary compounds with oestrogenic activity. An HBMOS is defined as a quotient of estimated daily intakes weighted by the relative in vivo potencies of these compounds. The Existing Chemicals Programme of the European Union provides Human and Environmental Risk Assessments of Existing Chemicals which include human exposure scenarios. Such exposure scenarios, along with potency estimates for endocrine activities, may provide a basis for a quantitative comparison of the potential endocrine-modulating effects of industrial chemicals with endocrine modulators as natural constituents of human diet. Natural phyto-oestrogens exhibit oestrogenic activity in vitro and in vivo. Important phyto-oestrogens for humans are isoflavones (daidzein, genistein) and lignans, with the highest quantities found in soybeans and flaxseed, respectively. Daily isoflavone exposures calculated for infants on soy-based formulae were in the ranges of 4.5-8 mg/kg body wt.; estimates for adults range up to 1 mg/kg body wt. The Senate Commission on the Evaluation of Food Safety (SKLM) of the Deutsche Forschungsgemeinschaft has also indicated a wide range of dietary exposures. For matters of risk assessment, the SKLM has based recommendations on dietary exposure scenarios, implying a daily intake of phyto-oestrogens in the order of 1 mg/kg body wt. On the basis of information compiled within the Existing Chemicals Programme of the EU, it appears that a daily human exposure to nonylphenol of 2 microg/kg body wt. may be a worst-case assumption, but which is based on valid scenarios. The intake of octylphenol is much lower, due to a different use pattern and applications, and may be neglected.

Data from migration studies led to estimations of the daily human uptake of bisphenol A of maximally 1 microg/kg body wt. On the basis of comparative data from uterotrophic assays in rats, with three consecutive days of oral applications involved, and taking the natural phyto-oestrogen daidzein as reference (= 1), relative uterotrophic activities in DA/Han rats follow the sequence: daidzein = 1; bisphenol A = 1; p-tert-octylphenol = 2; o, p'-DDT = 4; ethinyl oestradiol = 40,000. The derived values from exposure scenarios, as well as these relative potency values and bridging assumptions, led to calculations of HBMOS as a quantitative comparison of potential endocrine-modulating effects of industrial chemicals with those of natural constituents of human diet. HBMOS estimates for nonylphenol ranged between 250 and 500, dependent on bridging assumptions, and around 1000 for bisphenol A. The derivations of HBMOS were in full support of the conclusions reached by the SKLM of the Deutsche Forschungsgemeinschaft. The estimated HBMOS values for the industrial chemicals (nonylphenol, bisphenol A) appear sufficiently high to ensure the absence of a practical risk to human health under the present exposure conditions.

### Bibliographic Information

**A novel treatment for lupus nephritis: lignan precursor derived from flax.** Clark W F; Muir A D; Westcott N D; Parbtani A Department of Medicine, London Health Sciences Centre and The

University of Western Ontario, Canada. william.clark@lhsc.on.ca Lupus (2000), 9(6), 429-36. Journal code: 9204265. ISSN:0961-2033. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 10981647 AN 2001088332 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

**BACKGROUND:** Flaxseed has renoprotective effects in animal and human lupus nephritis. We have recently extracted the lignan precursor (secoisolariresinol diglucoiside) (SDG) to determine if this more palatable derivative of flaxseed would exert renoprotection similar to the whole flaxseed in the aggressive MRL/lpr lupus mouse model. **METHODS:** 131 MRL/lpr mice were randomly assigned to saline gavage, 600, 1,200 and 4,800 microg lignan gavage groups. At 7 weeks, 6 animals underwent platelet aggregating factor (PAF) lethal challenge and 40 were studied with urine collection to determine the levels of secoisolariresinol, enterodiol and enterolactone in the gavaged animals. A baseline study of 10 saline gavaged animals took place at 6 weeks. 25 animals in the saline gavage, 600 and 1200 microg lignan groups were studied at 14 and 22 weeks for GFR, spleen lymphocyte S-phase and organ weight studies. **RESULTS:** Metabolic studies indicated that secoisolariresinol is the major metabolite absorbed and the lowest lignan dose provides a lengthening in survival for the PAF lethal challenge. Body weight, fluid and water intake studies demonstrated that the lignan was well tolerated. Changes in proteinuria, GFR and renal size showed a time- and dose-dependent protection for the lignan precursor. Cervical lymph node size and spleen lymphocyte cells in the S-phase demonstrated modest dose-dependent reductions in the lignan gavaged groups. **CONCLUSION:** SDG was converted in the gut to secoisolariresinol, which was absorbed and well tolerated by the MRL/lpr mice. Renoprotection was evidenced, in a dose-dependent fashion, by a significant delay in the onset of proteinuria with preservation in GFR and renal size. This study suggests that SDG may have a therapeutic role in lupus nephritis.

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**Plasma insulin-like growth factor I levels in rats are reduced by dietary supplementation of flaxseed or its lignan secoisolariciresinol diglycoside.** Rickard S E; Yuan Y V; Thompson L U Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, 150 College Street, Ontario M5S 3E2, Toronto, Canada Cancer letters (2000), 161(1), 47-55. Journal code: 7600053. ISSN:0304-3835. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11078912 AN 2001065634 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

Flaxseed and its lignan secoisolariciresinol diglycoside (SDG) inhibit mammary tumor development in rats. Increased plasma insulin-like growth factor I (IGF-I) concentrations are associated with increased breast cancer risk. Therefore, the effect of flaxseed (5%) or SDG (1.5 mg/day) supplementation on plasma IGF-I levels was examined in rats treated with or without N-methyl-N-nitrosourea (MNU). In MNU-free rats, flaxseed and SDG reduced plasma IGF-I levels, which were inversely related to urinary lignan excretion. Only flaxseed significantly reduced plasma IGF-I concentrations in MNU-treated rats. The anticancer effect of flaxseed and SDG may be related, in part, to reductions in plasma IGF-I.

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**Experimental studies on lignans and cancer.** Thompson L U Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Ontario, Canada Bailliere's clinical endocrinology and metabolism (1998), 12(4), 691-705. Journal code: 8704785. ISSN:0950-351X. Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW); (REVIEW, TUTORIAL) written in English. PubMed ID 10384820 AN 1999312814 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

## Abstract

Mammalian lignans are produced from plant precursors such as secoisolariciresinol diglycoside (SDG) and matairesinol via the action of bacteria in the human or animal colon. While precursors are found in many plant foods, flaxseed is the richest source of SDG and was therefore used as a model to determine the anti-cancer effects of lignans. This paper reviews the experimental studies in animals and humans demonstrating the anti-cancer effects of flaxseed and its SDG as well as other studies relevant to the clinical use of lignans, such as those on their food sources, bio-availability and safety.

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**Effects of soy or rye supplementation of high-fat diets on colon tumour development in azoxymethane-treated rats.** Davies M J; Bowey E A; Adlercreutz H; Rowland I R; Rumsby P C  
BIBRA International, Woodmansterne Road, Carshalton, Surrey SM5 4DS, UK Carcinogenesis  
(1999), 20(6), 927-31. Journal code: 8008055. ISSN:0143-3334. Journal; Article; (JOURNAL  
ARTICLE) written in English. PubMed ID 10357769 AN 1999286174 MEDLINE (Copyright (C)  
2005 U.S. National Library of Medicine on SciFinder (R))

## Abstract

Evidence is accumulating that a diet high in plant-derived foods may be protective against cancer. One class of plant component under increasing investigation is the phytoestrogens of which there are two main groups: the isoflavones, found mainly in soy products, and the lignans, which are more ubiquitous and are found in fruit, vegetables and cereals with high levels being found in flaxseed. In this study, we have used carefully balanced high-fat (40% energy) diets: a control diet (containing low isoflavone soy protein as the sole protein source), a rye diet (the control diet supplemented with rye bran) and a soy diet (containing as protein source a high isoflavone soy protein). The effect of these diets on the development of colonic cancer was studied in F-344 rats treated with the carcinogen, azoxymethane (two doses of 15 mg/kg given 1 week apart). Colons from treated animals were examined for aberrant crypt foci (ACF) and tumours after 12 and 31 weeks. Results after 12 weeks showed no differences in the total number of ACF in the control, soy or rye bran groups. However, the soy group had increased numbers of small ACF (less than four crypts/focus) while the rye group had decreased numbers of large ACF (greater than six crypts/focus). Examination of colons after 31 weeks gave similar low numbers of ACF in each group with no differences in multiplicity. There were no differences in the number of tumours between the control (1.36 tumours/rat) and soy (1.38 tumours/rat) groups. However, there was a significant decrease in the number of tumours in the rye group (0.17 tumours/rat). These results suggest that soy isoflavones have no effect on the frequency of colonic tumours in this model while rye bran supplementation decreases the frequency of colon cancer. This effect is due not to a decrease in early lesions but in their progression to larger multi-crypt ACF. The study also supports the hypothesis that larger ACF are more predictive of subsequent tumorigenicity.

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**Phytoestrogens and human health effects: weighing up the current evidence.** Humfrey C D  
Astra Safety Assessment, Astra Charnwood, Loughborough, Leicester, UK. cdnh1@le.ac.uk  
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(JOURNAL ARTICLE); General Review; (REVIEW); (REVIEW, TUTORIAL) written in English.  
PubMed ID 9888630 AN 1999103705 MEDLINE (Copyright (C) 2005 U.S. National Library of  
Medicine on SciFinder (R))

## Abstract

Phytoestrogens are naturally occurring plant compounds which have oestrogenic and/or

anti-oestrogenic activity. They are present in many human foodstuffs including beans, sprouts, cabbage, spinach, soyabean, grains and hops. The main classes are the isoflavones, coumestans and lignans. This review assesses the evidence that these substances may have adverse and/or beneficial impacts on the risk of several hormone-dependent diseases in humans. Evidence from studies of various animal species has demonstrated that ingestion of high levels of phytoestrogens can produce adverse effects on reproductive endpoints including fertility. Studies in laboratory animals have also shown that exposure to high doses of phytoestrogens during development can adversely affect brain differentiation and reproductive development in rodents, but may also have possible beneficial effects. In humans, there is a lack of information concerning the possible effects of high doses of phytoestrogens in infants and this should be addressed as a matter of priority so that any risks (or benefits) can be established. In adults, no current data exist to suggest that consumption of phytoestrogens at the levels normally encountered in the diet is likely to be harmful. Epidemiological studies suggest that foodstuffs containing phytoestrogens may have a beneficial role in protecting against a number of chronic diseases and conditions. For cancer of the prostate, colon, rectum, stomach and lung, the evidence is most consistent for a protective effect resulting from a high intake of grains, legumes, fruits and vegetables; it is not possible to identify particular food types or components that may be responsible. Dietary intervention studies indicate that in women soya and linseed may have beneficial effects on the risk of breast cancer and may help to alleviate postmenopausal symptoms.

For osteoporosis, tentative evidence suggests phytoestrogens may have similar effects in maintaining bone density to those of the related pharmaceutical compound ipriflavone. Soya also appears to have beneficial effects on blood lipids which may help to reduce the risk of cardiovascular disease and atherosclerosis. Generally, however, little evidence exists to link these effects directly to phytoestrogens; many other components of soya and linseed are biologically active in various experimental systems and may be responsible for the observed effects in humans. It is concluded that dietary phytoestrogens may have a role in the prevention of several types of chronic disease including certain cancers. However, at present the evidence is not sufficient to recommend particular dietary practices or changes. Encouraging findings from laboratory and clinical studies indicate the need for further research to clarify the biological activities of phytoestrogens in humans.

### **Bibliographic Information**

**Flaxseed and its mammalian lignan precursor cause a lengthening or cessation of estrous cycling in rats.** Orcheson L J; Rickard S E; Seidl M M; Thompson L U Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Ontario, Canada Cancer letters (1998), 125(1-2), 69-76. Journal code: 7600053. ISSN:0304-3835. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9566698 AN 1998226350 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

Flaxseed and its mammalian lignan precursor secoisolariciresinol diglycoside (SDG) have been shown to be mammary cancer-protective in rats. Thus, the antiestrogenic effects of flaxseed and SDG were compared with tamoxifen, an antiestrogen, by monitoring rat estrous cycling. Four-week supplementation of a high-fat diet with flaxseed (2.5, 5, or 10%) or SDG (0.75, 1.5 or 3.0 mg/day) produced a dose-related cessation or lengthening (by 18-39%) of estrous cycles in up to 66% of rats. With tamoxifen (1 mg/kg body weight/day), 83% of the animals had irregular cycles or were in persistent diestrus. Flaxseed and SDG were antiestrogenic without gross tissue toxicity.

### **Bibliographic Information**

**Dietary flax seed in prevention of hypercholesterolemic atherosclerosis.** Prasad K Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, Canada Atherosclerosis (1997), 132(1), 69-76. Journal code: 0242543. ISSN:0021-9150. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9247361 AN 97388527 MEDLINE

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### **Abstract**

Oxygen free radicals (OFRs) have been implicated in the development of hypercholesterolemic atherosclerosis. 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. The effects of dietary flax seed on a high cholesterol diet induced atherosclerosis, lipid profile and OFR-producing activity of PMNLs (PMNL-CL) were investigated in rabbits. The rabbits were divided into 4 groups: group I, control; group II, flax seed diet (7.5 g/kg daily, orally); group III, 1% cholesterol diet; and group IV, same as group III but received flax seed (7.5 g/kg daily, orally). Blood samples were collected before and after 4 and 8 weeks on their respective diets for biochemical measurements and aortae were removed at the end of 8 weeks for estimation of atherosclerotic changes. The high cholesterol diet increased the serum level of total cholesterol (TC) and PMNL-CL without altering the levels of serum triglycerides (TG). These changes were associated with a marked development of atherosclerosis in the aorta. 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.

### **Bibliographic Information**

**Dietary phytoestrogens.** Kurzer M S; Xu X Department of Food Science and Nutrition, University of Minnesota, St. Paul 55108, USA Annual review of nutrition (1997), 17 353-81. Journal code: 8209988. ISSN:0199-9885. Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW) written in English. PubMed ID 9240932 AN 97382941 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

Broadly defined, phytoestrogens include isoflavones, coumestans, and lignans. A number of these compounds have been identified in fruits, vegetables, and whole grains commonly consumed by humans. Soybeans, clover and alfalfa sprouts, and oilseeds (such as flaxseed) are the most significant dietary sources of isoflavones, coumestans, and lignans, respectively. Studies in humans, animals, and cell culture systems suggest that dietary phytoestrogens play an important role in prevention of menopausal symptoms, osteoporosis, cancer, and heart disease. Proposed mechanisms include estrogenic and antiestrogenic effects, induction of cancer cell differentiation, inhibition of tyrosine kinase and DNA topoisomerase activities, suppression of angiogenesis, and antioxidant effects. Although there currently are no dietary recommendations for individual phytoestrogens, there may be great benefit in increased consumption of plant foods.

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**The influence of flaxseed and lignans on colon carcinogenesis and beta-glucuronidase activity.** Jenab M; Thompson L U Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Ontario, Canada Carcinogenesis (1996), 17(6), 1343-8. Journal code: 8008055. ISSN:0143-3334. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed

ID 8681453 AN 96281696 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

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 whether over the long term flaxseed still exerts a colon cancer protective effect, whether its effect may, in part, be due to its high content of SD and whether any change in beta-glucuronidase activity plays a role in the protective effect. Six groups of male Sprague-Dawley rats were fed for 100 days either a basal high fat (20%) diet (BD), BD supplemented with 2.5 or 5% flaxseed or 2.5 or 5% defatted flaxseed (equivalent to the respective flaxseed diets) or BD with a daily gavage of 1.5 mg SD. All rats were injected with a single dose of azoxymethane (15 mg/kg body wt) 1 week prior to commencing the dietary treatments. Urinary lignan excretion, which is an indicator of mammalian lignan production, was significantly increased in the flaxseed and defatted flaxseed groups. The total activity of cecal beta-glucuronidase was significantly increased in a dose-dependent manner by the flaxseed and defatted flaxseed diet groups. Compared with the control the number of aberrant crypts per focus was significantly reduced in the distal colon of the treated rats. Four microadenomas and two polyps were observed in the control group, but not in the treated groups. The total activity of beta-glucuronidase was positively correlated with total urinary lignan excretion and negatively with the total number of aberrant crypts and the total number of aberrant crypt foci in the distal colon. There were no significant differences between the flaxseed and the corresponding defatted flaxseed groups. It is concluded 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.

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**Chemical studies of phytoestrogens and related compounds in dietary supplements: flax and chaparral.** Obermeyer W R; Musser S M; Betz J M; Casey R E; Pohland A E; Page S W Division of Natural Products, Food and Drug Administration, Washington, District of Columbia 20204 Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N. Y.) (1995), 208(1), 6-12. Journal code: 7505892. ISSN:0037-9727. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 7892296 AN 95199376 MEDLINE (Copyright (C) 2005 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

High-performance liquid chromatographic (HPLC) and mass spectrometric (MS) procedures were developed to determine lignans in flaxseed (*Linum usitatissimum*) and chaparral (*Larrea tridentata*). Flaxseed contains high levels of phytoestrogens. Chaparral has been associated with acute nonviral toxic hepatitis and contains lignans that are structurally similar to known estrogenic compounds. Both flaxseed and chaparral products have been marketed as dietary supplements. A mild enzyme hydrolysis procedure to prevent the formation of artifacts in the isolation step was used in the determination of secoisolariciresinol in flaxseed products. HPLC with ultraviolet spectral (UV) or MS detection was used as the determinative steps. HPLC procedures with UV detection and mass spectrometry were developed to characterize the phenolic components, including lignans and flavonoids, of chaparral and to direct fractionation studies for the bioassays.

### **Bibliographic Information**

**Flaxseed Oil and Bone Development in Growing Male and Female Mice.** Cohen, Stacey; Ward, Wendy. Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Can. Journal of Toxicology and Environmental Health, Part A (2005), 68(21), 1861-1870. Publisher: Taylor & Francis, Inc., CODEN: JTEHF8 ISSN: 1528-7394. Journal

written in English. AN 2005:1092612 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### Abstract

Flaxseed is being increasingly incorporated into foods as a result of its proposed health benefits. Combined with the fact that bone is sensitive to dietary changes in fatty acids, the optimization of bone metab. during childhood may be influenced by altering the type and amts. of fatty acids consumed. The effects of whole flaxseed or its purified lignan on bone development have been investigated, but pos. and/or neg. effects of flaxseed oil (FO), rich in  $\alpha$ -linolenic acid (ALA), on bone development have not been reported. The objective of this study was to elucidate the effects of a 10% FO diet on indexes of bone health, including bone mass and biomech. bone strength. Male and female mice were fed either a 10% flaxseed oil (FO) or a 10% corn oil (CO) diet from postnatal day (PND) 28 until PND 91. Male and female mice fed FO converted ALA to eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) as indicated by significantly higher serum EPA and DHA; however, serum cytokines (interleukin-1 $\beta$ , interleukin-6, tumor necrosis factor- $\alpha$ ) with the potential to modulate bone metab. did not significantly differ among groups. As expected, serum linoleic acid and arachidonic acid were significantly lower among mice fed FO. Feeding FO diet did not result in a higher or lower bone mass or stronger or weaker femurs and lumbar vertebra than in mice fed CO diet in either gender, suggesting that the level of ALA attainable in a 10% flaxseed oil diet is safe with regard to bone development in growing mice.

### Bibliographic Information

**Enterolactone induces apoptosis and inhibits growth of colo 201 human colon cancer cells both in vitro and in vivo.** Danbara, Naoyuki; Yuri, Takashi; Tsujita-Kyutoku, Miki; Tsukamoto, Reiko; Uehara, Norihisa; Tsubura, Airo. Department of Pathology II, Kansai Medical University, Osaka, Japan. *Anticancer Research* (2005), 25(3B), 2269-2276. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 143:146103 AN 2005:639302 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### Abstract

**Background:** The mammalian lignan enterolactone (ENL) is produced from plant lignans which are present in large amts. in flaxseed (linseed). The effect of ENL on colon cancer cell growth in vitro and in vivo, and its mechanisms of action, have not been studied in detail. **Materials and Methods:** The growth of the colo 201 human colon cancer cell line was examd. by colorimetric 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay, while the expression of apoptosis- and proliferation-related proteins (p53, Bax, Bcl-xL and S, Bcl-2, Caspase-8, Caspase-3 and proliferating cell nuclear antigen (PCNA)) were examd. by Western blotting. In vivo tumor growth was examd. by transplanting colo 201 cells into ENL-treated and placebo treated athymic mice. **Results:** The MTS assay showed that ENL suppressed colo 201 cell growth (IC50 for 72 h: 118.4  $\mu$ M) in vitro. On flow cytometry, induction of apoptosis was confirmed by the appearance of subG1 populations, while cell cycle progression was not affected. The expression of an apoptosis-suppressing protein (Bcl-2) was down-regulated, an apoptosis-enhancing protein (cleaved form of Caspase-3) was up-regulated, proliferation-related PCNA protein was down-regulated and p53, Bax, Bcl-xL and S and Caspase-8 levels were unchanged. ENL, at a dose of 10 mg/kg given 3 times per wk by s.c. injection, significantly inhibited the growth of colo 201 cells transplanted into athymic mice without any adverse effects. **Conclusion:** ENL suppressed colo 201 human colon cancer cell growth both in vitro and in vivo. The tumor-suppressing mechanisms included apoptosis and decreased cell proliferation.

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**Effect of chronic administration of lignan complex isolated from flaxseed on the hemopoietic system.** Prasad, Kailash. Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, Can. *Molecular and Cellular Biochemistry* (2005),

270(1&2), 139-145. Publisher: Springer, CODEN: MCBIB8 ISSN: 0300-8177. Journal written in English. CAN 142:456635 AN 2005:234606 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### **Abstract**

Lignan complex has been isolated from flaxseed. It has been shown to reduce serum lipids and the extent of hypercholesterolemic atherosclerosis. However, it is not known whether the chronic use of lignan complex has any adverse effects on the hemopoietic system. The effects of lignan complex (40 mg/kg body wt orally daily for 2 mo) on the red blood cells (RBC) count, mean corpuscular vol. (MCV), red cell distribution width (RDW), hematocrit (Hct), Hb, mean corpuscular Hb (MCH), mean corpuscular Hb concn. (MCHC), and counts of white blood cell (WBC), granulocytes, lymphocytes, monocytes and platelet, and platelet vol. were investigated in normo- and hypercholesterolemic rabbits. The results show that lignan complex had no adverse effects of counts of RBC, WBC, granulocytes, lymphocytes, monocytes and platelet in both the normo- and hyper-cholesterolemic rabbits. The values for MCV, RDW, Hct, Hb, MCH, MCHC, and platelet vol. were similar in lignan complex-treated or untreated normo- and hypercholesterolemic rabbits. It is concluded that chronic use of lignan complex had no adverse effects on the hemopoietic system.

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**Phytoestrogens for osteoporosis.** Button, Brenna J.; Patel, Nima. University of Missouri-Kansas City School of Pharmacy, Kansas City, MO, USA. *Clinical Reviews in Bone and Mineral Metabolism* (2004), 2(4), 341-356. Publisher: Humana Press Inc., CODEN: CRBMBF ISSN: 1534-8644. Journal; General Review written in English. CAN 142:372970 AN 2005:86817 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### **Abstract**

A review. Phytoestrogens are plant-derived compds. with estrogenic activity found in natural dietary sources. Common phytoestrogen sources include soybeans, soy products, alfalfa fodder, flaxseed, and over-the-counter dietary supplements. This article summarizes the clin. evidence available regarding the bone-altering effects of phytoestrogens in humans, provides guidance as to their potential application in therapy, and briefly describes other uses of phytoestrogens. Evidence that phytoestrogens may provide some pos. bone-altering effects is promising, but the full understanding of their efficacy and safety is not completely investigated yet. Some bone-sparing effects have been demonstrated with natural and com. phytoestrogens and the synthetic Ipriflavone through limited studies. New research involving com. phytoestrogen contg. products such as Promensil, Rimostil, Tofupill/Femarelle, and the synthetic ipriflavone attempt to address unanswered questions. Research has yielded pos., yet inconsistent, trends with respect to bone turnover markers, bone mineral d., and bone mineral content, but little fracture data exists. Adequate phytoestrogen dosages have yet to be detd.; except 200 mg of ipriflavone three times a day is an established dosage in most trials. Inconsistency in pos. results also exists for menopausal symptoms and breast cancer, although evidence is established for redn. of cardiovascular disease. In light of better established drug products, phytoestrogens should not be recommended at this time as first-line therapy for prevention or treatment of osteoporosis in men or women because questions remain regarding product selection and the degree of efficacy and safety. Health care providers must stay current with key research and continue to provide important patient education regarding the therapeutic use and safety of phytoestrogens for osteoporosis.

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### Patent Family Information

| Patent No.                  | Kind | Date  | Application No.  | Date     |
|-----------------------------|------|---|------------------|----------|
| EP 1500695                  | A1   | 20050126  | EP 2004-17478    | 20040723 |
|                             |      | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR |                  |          |
| DE 10333858                 | A1   | 20050224  | DE 2003-10333858 | 20030724 |
| <u>Priority Application</u> |      |   |                  |          |
| DE 2003-10333858            | A    | 20030724  |                  |          |

### Abstract

The procedure for processing of plant oils (such as flax or perilla oil) contg. toxic components comprises the following steps: (a) mixing the oil with alc. at 15-40°; (b) optionally, filtration; (c) phase sepn. under sepn. of the alc. fraction; (d) optionally,  $\geq 1$  post-washing process with subsequent phase sepn.; and (e) optionally, removing the residual alc. from the oil by known methods, esp. vacuum distn. For pretreatment of glycoside-contg. oilseed (such as flax seed), it is mixed with alc. up to a complete uptake of the alc. As alc., esp. ethanol of concn. 50-96% is used. The glycoside conc. contg. lignan and lecithin is obtained after removing the alc. The oilseed cake is also processed.

### Bibliographic Information

**A thirteen week dietary toxicity study with 7-hydroxymatairesinol potassium acetate (HMRLignan) in rats.** Lina, B.; Korte, H.; Nyman, L.; Unkila, M. Department of Toxicology and Applied Pharmacology, TNO Nutrition and Food Research, Zeist, Neth. Regulatory Toxicology and Pharmacology (2005), 41(1), 28-38. Publisher: Elsevier, CODEN: RTOPLW ISSN: 0273-2300. Journal written in English. CAN 143:72904 AN 2005:25992 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### Abstract

Plant lignan 7-hydroxymatairesinol (7-HMR) is a novel precursor of the mammalian lignan enterolactone. A 13 wk toxicity study at dietary levels of 0, 0.25, 1, and 4% (wt./wt.) of potassium acetate complex of 7-HMR (HMRLignan) was conducted in the Wistar rat. These dietary levels resulted in an av. daily intake of 160, 640, and 2600 mg HMRLignan/kg body wt./day, resp. A considerable systemic exposure of HMRLignan was verified by dose-related increases in plasma total (conjugated and unconjugated) concn. of 7-HMR and metabolites enterolactone, 7-hydroxyenterolactone, and matairesinol. Enterolactone appeared to be the major metabolite. Most (>96%) of the circulating 7-HMR and enterolactone was in conjugated form as measured from the low-dose rat plasma samples. HMRLignan exposure did not significantly affect clin. signs, ophthalmoscopy or neurobehavioral observations, and motor activity. Transient redns. in food intake and body wt. gain in the mid- and high-dose group were ascribed to decreased palatability of the test feed. Only in males of the high-dose group the body wts. remained slightly reduced throughout the study. In the high-dose group the no. of thrombocytes (females), and total white blood cell count (males) were increased. Plasma triglycerides were dose-dependently depressed in males of all test groups and in females of the mid- and high-dose group, while plasma total cholesterol, and phospholipids were decreased in high-dose males. These changes, which have

also been reported for other (flaxseed) lignans, were not considered to represent adverse effects. The relative wt. of the kidneys was increased in males of the high-dose group. The wt. of the full and empty cecum showed dose-related increases in males of all treatment groups and in females of the high-dose group. Abs. ovary wts. were decreased in all treatment groups while decreases in relative ovary wts. were confined to the mid- and high-dose group. In addn., a marginal lengthening of the estrus cycle was noted in high-dose females.

Apart from prevention of hyaline droplet nephropathy in all high-dose male rats, there were no treatment-related histopathol. alterations. It was concluded that HMRLignan showed weak antiestrogen-like activity which may be mediated through enterolactone metabolite. Based on declined ovary wt., the no obsd. adverse effect level of HMRLignan was set at 0.25% in feed corresponding to 160 mg/kg body wt./day.

### **Bibliographic Information**

**The effects of dietary flaxseed on the Fischer 344 rat: II. Liver  $\gamma$ -glutamyltranspeptidase activity.** Hemmings, Susan J.; Westcott, Neil; Muir, Alister; Czechowicz, Dominika. Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, SK, Can. Cell Biochemistry and Function (2004), 22(4), 225-231. Publisher: John Wiley & Sons Ltd., CODEN: CBFUDH ISSN: 0263-6484. Journal written in English. CAN 141:295273 AN 2004:576108 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### **Abstract**

The effect of 10% flax chow consumption from the 30th to the 130th day after birth was examd. in male Fischer 344 rats. The effects of both the high lignan/high oil Norlin strain and a high lignan/low oil Solin strain of flaxseed were compared. Phys. and behaviorally there were no differences in rats belonging to the three dietary groups at any time. At 50 and 100 days of dietary exposure, blood glucose levels were the same in Norlin and Solin flax chow-fed and as well as regular chow-fed rats; there were no signs of toxicity in the Norlin and Solin flax-fed rats since their plasma levels of alanine aminotransferase were the same and equal to those of regular chow-fed rats. The activity of  $\gamma$ -glutamyltranspeptidase ( $\gamma$ GT) displayed an increase in the liver homogenates of flax chow-fed rats. This increase was the same in Norlin and Solin flax-fed rats at 50 and 100 days. Thus the liver effect was not oil, but lignan, likely secoisolariciresinol diglucoside (SDG), induced and was effected early on, and sustained, after flax exposure. The degree of heat activation of liver homogenate  $\gamma$ GT was the same in regular chow-fed and flax chow-fed rats. Compared to liver homogenate  $\gamma$ GT activity, the sol. form of  $\gamma$ GT was expressed at very low levels while the plasma membrane-bound form of  $\gamma$ GT was expressed at very high levels in rat liver in both regular chow-fed and flax chow-fed rats. There was no effect of flax feeding on the sol. form of liver  $\gamma$ GT which was expressed at a very low level. Flax feeding effected an increase in the activity of  $\gamma$ GT in isolated plasma membrane fractions which mirrored that in liver homogenates: the same degree of increase was seen in Norlin flax chow-fed and Solin flax chow-fed rats. Flax consumption effects an increase in the activity of liver  $\gamma$ GT at the level of the plasma membrane which is lignan dependent, physiol. relevant and may be linked to hepatoprotection against injury through an increase in reduced glutathione.

### **Bibliographic Information**

**The effects of dietary flaxseed on the Fischer 344 rat: I. Development, behaviour, toxicity and the activity of liver  $\gamma$ -glutamyltranspeptidase.** Hemmings, Susan J.; Barker, Lorraine. Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, SK, Can. Cell Biochemistry and Function (2004), 22(2), 113-121. Publisher: John Wiley & Sons Ltd., CODEN: CBFUDH ISSN: 0263-6484. Journal written in English. CAN 141:22836 AN 2004:251451 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### **Abstract**

The effects of exposure to, followed by consumption of, 10% flax chow fed from the 18th day of gestation to the 86th day after birth were examd. in male and female F-344 rats. Growth curves of the flax chow-fed and regular chow-fed rats were identical, as were developmental milestones, such as pinna development, growth of hair, and eye opening. Acoustical startle and the righting reflexes as developmental behavioral indexes were also the same. Blood glucose levels were comparable in flax chow-fed and regular chow-fed rats at all stages of development, indicating that flax was without effect on glucose balance. There were no signs of toxicity in the flax chow-fed rats since their blood plasma levels of alanine aminotransferase and  $\gamma$ -glutamyltranspeptidase ( $\gamma$ GT) were the same as in regular chow-fed rats. The activity of  $\gamma$ GT was increased in the liver of flax chow-fed rats after puberty, more in the males (4-fold) than in females (1.38-fold). This is suggestive of an estrogenic effect from the estrogenic flax lignans. The beneficial effect of the flax-induced increase in liver  $\gamma$ GT is discussed. Thus, dietary 10% flax chow is without long-term effects on growth, development and behavior, is non-toxic, and may be hepatoprotective.

#### **Bibliographic Information**

**Flaxseed constituents and human health.** Muir, Alister D.; Westcott, Neil D. Bioproducts and Processing Saskatoon Research Center, Agriculture and Agri-Food Canada, Saskatoon, SK, Can. Medicinal and Aromatic Plants--Industrial Profiles (2003), 34(Flax), 243-251. Publisher: Taylor & Francis Ltd., CODEN: MAPPFL ISSN: 1027-4502. Journal; General Review written in English. CAN 141:70696 AN 2003:1014244 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

#### **Abstract**

A review on the biol. activity of some components of flaxseed and related members of the Linum genus. Antinutrients, a vitamin B6 antagonist, gums, proteins, lignans, and acute and chronic toxicol. aspects are discussed.

#### **Bibliographic Information**

**Exposure to flaxseed or its purified lignan during suckling inhibits chemically induced rat mammary tumorigenesis.** Chen, Jianmin; Tan, Kah Poh; Ward, Wendy E.; Thompson, Lillian U. Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Can. Experimental Biology and Medicine (Maywood, NJ, United States) (2003), 228(8), 951-958. Publisher: Society for Experimental Biology and Medicine, CODEN: EBMMBE ISSN: 1535-3702. Journal written in English. CAN 140:4448 AN 2003:732746 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

#### **Abstract**

Feeding flaxseed (FS) or its lignan secoisolariciresinol diglucoside (SDG) to rat dams during lactation enhances differentiation of the mammary gland in the female rat offspring. This study detd. whether exposure to diets with 10% FS or SDG (equiv. to the amt. in 10% FS diet) during suckling could protect against 9,10-dimethyl-1,2-benzanthracene (DMBA)-induced rat mammary tumorigenesis later in life. Dams were fed the AIN-93G basal diet (BD) throughout pregnancy. After delivery, the dams continued on BD or were fed BD supplemented with 10% FS or SDG during lactation. Dam urine 3-day samples were analyzed for mammalian lignans (enterodiol, enterolactone, secoisolariciresinol). After weaning, all female offspring were fed BD. At postnatal days 49-51, during proestrus phase, offspring were gavaged with 5 mg DMBA. Compared with the BD group at 21 wk post-DMBA administration, the FS and SDG groups had lower tumor incidence (31.3 and 42.0% lower, resp.), total tumor load (50.8 and 62.5% lower, resp.), mean tumor size (43.9 and 67.7% lower, resp.), and tumor no. (46.9 and 44.3% lower, resp.) per rat. There was a decreasing trend in final tumor wts. in rats fed FS or SDG. The high urinary lignan excretion in dams fed FS or SDG corresponded with the decreased tumor development. The FS and SDG

groups did not much differ in tumor indexes, indicating that the effect of FS is primarily due to its SDG. There were no significant changes in selective reproductive indexes measured among dams and offspring. Thus, exposure to FS or SDG during suckling suppressed DMBA-induced rat mammary tumorigenesis, suggesting that exposure to lignans at this early stage of mammary gland development can decrease the susceptibility to mammary carcinogenesis later in life without adverse effects on selective reproductive indexes in dams or female offspring.

#### **Bibliographic Information**

**Flaxseed lignans: health benefits, bioavailability, and safety.** Thompson, Lilian U.; Ward, Wendy E. Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Can. Editor(s): Gilani, G. Sarwar; Anderson, John J. B. *Phytoestrogens and Health* (2002), 405-426. Publisher: AOCS Press, Champaign, Ill CODEN: 69DHA5 Conference; General Review written in English. CAN 139:84410 AN 2002:881575 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

#### **Abstract**

A review. The health benefits, bioavailability, and safety of dietary flaxseed lignans in humans are discussed. The ability of lignans to decrease the risk of cancer, cardiovascular diseases, diabetes mellitus, kidney diseases, osteoporosis, and menopausal symptoms is discussed.

#### **Bibliographic Information**

**Dietary estrogens of plant and fungal origin: Occurrence and exposure.** Ward, W. E.; Thompson, L. U. Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Can. Editor(s): Metzler, Manfred. *Handbook of Environmental Chemistry* (2001), 3(Pt. L), 101-128. Publisher: Springer, Berlin, Germany CODEN: 45NZAP Conference; General Review written in English. CAN 136:324610 AN 2002:206527 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

#### **Abstract**

A review. Phytoestrogens and mycoestrogens are naturally occurring dietary compds. that strongly resemble the structure of the mammalian steroidal estrogens. Lignans, isoflavones, and coumestans are the three major classes of phytoestrogens to which humans and animals are exposed. Animals may be exposed to high levels of phytoestrogens while grazing in pastures or consuming feed rich in clover or alfalfa. Domestic livestock may be exposed to mycoestrogens, primarily zearalenone, by consuming feed that is contaminated with *Fusarium* spp. toxins. Livestock consuming feed is exposed to 907 - 1195 mg of isoflavones/kg of feed. In clover pastures, livestock is exposed to isoflavones at a level of 0.05 - 4.8% (dry wt.). Mycoestrogen exposure varies according to the level of contamination of feed. The zearalenone content of animal feed is estd. to be within 14 - 215 ng/g depending on the geog. region and type of grain or cereal consumed. With respect to human exposure, lignans and isoflavones are most commonly found in foods contg. flaxseed or soybeans, resp. Since the extent of phytoestrogen exposure is dependent on dietary compn., vegetarians or infants receiving soy-based infant formulas have a significantly higher level of exposure to phytoestrogens. Humans may be exposed to trace or low levels of mycoestrogens via consumption of cereal or cereal products that are mildly contaminated with zearalenone. Dietary intakes of zearalenone are estd. to be 100 - 500 ng/kg body wt. per day. Both animal and human studies have demonstrated that exposure to phytoestrogens and mycoestrogens can result in estrogen-like or antiestrogen-like effects depending on the timing of exposure in the life-cycle, the duration of exposure, and the dose administered. Accordingly, these compds. can have adverse effects or health benefits. Alterations in reproductive indexes that lead to reduced fertility rates have been reported in animals grazing in pastures contg. phytoestrogens or consuming feed contaminated with mycoestrogens.

Impairments in sexual behavior and alterations in measures of masculinity as well as modifications

in carcass compn. have been reported in animals implanted with a synthetic analog of zearalenone. In humans, the progression of diseases in which estrogen may play a role, such as cancer, cardiovascular disease, and osteoporosis, may be attenuated with phytoestrogen exposure. Exposure to phytoestrogens during crit. developmental periods may reduce the risk of disease development in later life.

### **Bibliographic Information**

**Exposure to flaxseed or its purified lignan during suckling only or continuously does not alter reproductive indices in male and female offspring.** Ward, Wendy E.; Chen, Jianmin; Thompson, Lilian U. Department of Nutritional Sciences, University of Toronto, Toronto, ON, Can. Journal of Toxicology and Environmental Health, Part A (2001), 64(7), 567-577. Publisher: Taylor & Francis, CODEN: JTEHF8 ISSN: 1528-7394. Journal written in English. CAN 136:183094 AN 2001:902397 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### **Abstract**

The objective of this study was to det. whether maternal feeding of flaxseed during lactation altered reproductive indexes in male and female offspring. Rat dams were fed basal diet (BD) or BD contg. either 10% flaxseed (10F) or the equiv. quantity of secoisolariciresinol diglycoside (SDG) present in the 10% (10S) flaxseed diet from the start of lactation until pups were 21 d old. At the end of lactation (postnatal day [PND] 21), suckling pups either continued on the mother's diet or were switched to BD until adolescence (PND 50) or young adulthood (PND 132) to det. if continuous exposure to flaxseed or SDG altered reproductive indexes. The reproductive indexes that were measured included anogenital distance from birth through PND 21, age and body wt. at puberty onset (females only), estrous cycle length, reproductive organ wts. at PND 50 and 132, and histol. anal. of reproductive organs (uterus, ovaries, prostate) at PND 132. There were no significant effects of exposing male or female offspring to flaxseed or SDG during suckling only or during suckling through the postsuckling period on any of the reproductive indexes measured. These findings are in contrast to the estrogenic effects obsd. in male and female offspring exposed to flaxseed during fetal life through suckling and suggest that fetal life is a more hormone-sensitive period of development. Although maternal feeding of flaxseed during lactation appears to be safe with respect to reproductive indexes among offspring, future investigation is required to elucidate whether there are any long-term implications with respect to fertility.

### **Bibliographic Information**

**The role of phytoestrogens in the prevention and treatment of osteoporosis in ovarian hormone deficiency.** Arjmandi, Bahram H. Department of Nutritional Sciences, Oklahoma State University, Stillwater, OK, USA. Journal of the American College of Nutrition (2001), 20(5, Suppl.), 398S-402S. Publisher: American College of Nutrition, CODEN: JONUDL ISSN: 0731-5724. Journal; General Review written in English. CAN 136:150350 AN 2001:784097 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### **Abstract**

A review. Ovarian hormone deficiency is a major risk factor for osteoporosis in postmenopausal women. Hormone replacement therapy (HRT) is perhaps the most effective treatment, as it has been demonstrated to both reduce the rate of bone loss and risk of fracture, including hip fracture. However, not all women who may benefit from HRT are willing to initiate this treatment due to fear of cancer and contraindications. Other therapeutic agents currently available are also assocd. with certain adverse effects. As a result, postmenopausal women are more inclined to use natural remedies to alleviate postmenopausal symptoms and help reduce their risk for chronic diseases such as osteoporosis. Recent reports support the notion that certain bioactive constituents, e.g., phytoestrogens, in plants play a role in maintaining or improving skeletal health. The main consumable plant sources of phytoestrogens include isoflavones and lignans found mainly in

soybeans and flaxseed, resp. Although this paper primarily focuses on the effects of soy protein or its isoflavones on bone, addnl. statements regarding the role of flaxseed and dried plums, a rich source of polyphenols, with respect to bone will be made.

### **Bibliographic Information**

**Exposure to flaxseed and its purified lignan reduces bone strength in young but not older male rats.** Ward, Wendy E.; Yuan, Yvonne V.; Cheung, Angela M.; Thompson, Lilian U. Department of Nutritional Sciences, University of Toronto, Toronto, ON, Can. *Journal of Toxicology and Environmental Health, Part A* (2001), 63(1), 53-65. Publisher: Taylor & Francis, CODEN: JTEHF8 ISSN: 1528-7394. Journal written in English. CAN 135:91957 AN 2001:342805 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### **Abstract**

Flaxseed is the richest source of the plant lignan secoisolariciresinol diglycoside (SDG), which is converted to the two major mammalian lignans, enterodiol (ED) and enterolactone (EL), by colonic bacteria. Because both ED and EL can produce biol. effects similar to estrogen, exposure to lignans during early stages of development may adversely alter the normal development of bone in males since bone is a hormone-sensitive tissue. To det. whether early exposure to flaxseed or its lignan compromised the acquisition of bone mass or reduced bone strength, male offspring were exposed to one of three diets during lactation only (birth through postnatal day [PND] 21) via mother's milk or continuously from the start of lactation through to adolescence (PND 50) or young adulthood (PND 132). The diets were a basal diet (BD) that was devoid of phytoestrogens, BD contg. 10% flaxseed, or BD contg. the equiv. quantity of SDG present in a 10% flaxseed diet. To assess bone quantity, the bone mineral content (BMC) and bone mineral d. (BMD) of femurs were assessed by dual-energy x-ray absorptiometry. Since the biomech. properties of bone are indicators of the microarchitecture and thus bone quality, the biomech. strength of femurs was assessed by three-point bending. At PND 50, ultimate bending stress and Young's modulus, measures of bone strength, were reduced among rats that received the 10% flaxseed diet from PND 0 through PND 50, while there were no marked differences in bone size, BMC, or BMD among groups. This effect does not appear to be due to the lignan in flaxseed, as continuous exposure to the diet contg. the equiv. quantity of lignan (10 S diet) did not alter any measures of bone strength. In contrast to PND 50, bone strength did not differ among groups at PND 132, indicating that the compromise in bone strength was not sustained into early adulthood. Bone size, BMC, and BMD continued to be similar among treatment groups at PND 132. Exposing male rats to a diet contg. 10% flaxseed or an equiv. quantity of lignan either during lactation only or through to early adulthood is safe with respect to bone health, as measures of bone mass and strength were similar to control rats.

### **Bibliographic Information**

**Comparative assessment of endocrine modulators with estrogenic activity: I. Definition of a hygiene-based margin of safety (HBMOS) for xeno-oestrogens against the background of European developments.** Bolt, Hermann M.; Janning, Petra; Michna, Horst; Degen, Gisela H. Institut für Arbeitsphysiologie an der Universität Dortmund, Dortmund, Germany. *Archives of Toxicology* (2001), 74(11), 649-662. Publisher: Springer-Verlag, CODEN: ARTODN ISSN: 0340-5761. Journal; General Review written in English. CAN 134:261901 AN 2001:52676 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### **Abstract**

A review with many refs. A novel concept - the hygiene-based margin of safety (HBMOS) - is suggested for the assessment of the impact of potential endocrine modulators. It integrates exposure scenarios and potency data for industrial chems. and naturally occurring dietary compds. with estrogenic activity. An HBMOS is defined as a quotient of estd. daily intakes weighted by the

relative in vivo potencies of these compds. The Existing Chems. Program of the European Union provides Human and Environmental Risk Assessments of Existing Chems. which include human exposure scenarios. Such exposure scenarios, along with potency ests. for endocrine activities, may provide a basis for a quant. comparison of the potential endocrine-modulating effects of industrial chems. with endocrine modulators as natural constituents of human diet. Natural phyto-estrogens exhibit estrogenic activity in vitro and in vivo. Important phyto-estrogens for humans are isoflavones (daidzein, genistein) and lignans, with the highest quantities found in soybeans and flaxseed, resp. Daily isoflavone exposures calcd. for infants on soy-based formulas were in the ranges of 4.5-8 mg/kg body wt.; ests. for adults range up to 1 mg/kg body wt. The Senate Commission on the Evaluation of Food Safety (SKLM) of the Deutsche Forschungsgemeinschaft has also indicated a wide range of dietary exposures. For matters of risk assessment, the SKLM has based recommendations on dietary exposure scenarios, implying a daily intake of phyto-estrogens in the order of 1 mg/kg body wt. On the basis of information compiled within the Existing Chems. Program of the EU, it appears that a daily human exposure to nonylphenol of 2 mg/kg body wt. may be a worst-case assumption, but which is based on valid scenarios. The intake of octylphenol is much lower, due to a different use pattern and applications, and may be neglected. Data from migration studies led to estns. of the daily human uptake of bisphenol A of maximally 1 mg/kg body wt.

On the basis of comparative data from uterotrophic assays in rats, with three consecutive days of oral applications involved, and taking the natural phyto-estrogen daidzein as ref. (=1), relative uterotrophic activities in DA/Han rats follow the sequence: daidzein = 1; bisphenol A = 1;p-tert-octylphenol = 2;o,p'-DDT = 4; ethinyl estradiol = 40,000. The derived values from exposure scenarios, as well as these relative potency values and bridging assumptions, led to calcns. of HBMOs as a quant. comparison of potential endocrine-modulating effects of industrial chems. with those of natural constituents of human diet. HBMOs ests. for nonylphenol ranged between 250 and 500, dependent on bridging assumptions, and around 1000 for bisphenol A. The derivations of HBMOs were in full support of the conclusions reached by the SKLM of the Deutsche Forschungsgemeinschaft. The estd. HBMOs values for the industrial chems. (nonylphenol, bisphenol A) appear sufficiently high to ensure the absence of a practical risk to human health under the present exposure conditions.

### **Bibliographic Information**

**A novel treatment for lupus nephritis: lignan precursor derived from flax.** Clark, W. F.; Muir, A. D.; Westcott, N. D.; Parbtani, A. Department of Medicine, The University of Western Ontario, London, ON, Can. *Lupus* (2000), 9(6), 429-436. Publisher: Nature Publishing Group, CODEN: LUPUES ISSN: 0961-2033. Journal written in English. CAN 134:95286 AN 2000:599065 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

### **Abstract**

Flaxseed has renoprotective effects in animal and human lupus nephritis. The authors have recently extd. the lignan precursor (secoisolariciresinol diglucoside) (SDG) to det. if this more palatable deriv. of flaxseed would exert renoprotection similar to the whole flaxseed in the aggressive MRL/lpr lupus mouse model. Methods: 131 MRL/lpr mice were randomly assigned to saline gavage, 600, 1200 and 4800 µg lignan gavage groups. At 7 wk, 6 animals underwent platelet aggregating factor (PAF) lethal challenge and 40 were studied with urine collection to det. the levels of secoisolariciresinol, enterodiol and enterolactone in the gavaged animals. A baseline study of 10 saline gavaged animals took place at 6 wk. 25 Animals in the saline gavage, 600 and 1200 µg lignan groups were studied at 14 and 22 wk for GFR, spleen lymphocyte S-phase and organ wt. studies. Results: Metabolic studies indicated that secoisolariciresinol is the major metabolite absorbed and the lowest lignan dose provides a lengthening in survival for the PAF lethal challenge. Body wt., fluid and water intake studies demonstrated that the lignan was well tolerated. Changes in proteinuria, GFR and renal size showed a time- and dose-dependent protection for the lignan precursor. Cervical lymph node size and spleen lymphocyte cells in the S-phase demonstrated modest dose-dependent redns. in the lignan gavaged groups. Conclusion:

SDG was converted in the gut to secoisolariresinol, which was absorbed and well tolerated by the MRL/lpr mice. Renoprotection was evidenced, in a dose-dependent fashion, by a significant delay in the onset of proteinuria with preservation in GFR and renal size. This study suggests that SDG may have a therapeutic role in lupus nephritis.

#### **Bibliographic Information**

**Flaxseed and its mammalian lignan precursor cause a lengthening or cessation of estrous cycling in rats.** Orcheson, Lindy J.; Rickard, Sharon E.; Seidl, Maja M.; Thompson, Lilian U. 150 College St., Faculty of Medicine, Department of Nutritional Sciences, University of Toronto, Toronto, Can. *Cancer Letters* (Shannon, Ireland) (1998), 125(1,2), 69-76. Publisher: Elsevier Science Ireland Ltd., CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 128:252593 AN 1998:101229 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

#### **Abstract**

Flaxseed and its mammalian lignan precursor secoisolariresinol diglycoside (SDG) have been shown to be mammary cancer-protective in rats. Thus, the antiestrogenic effects of flaxseed and SDG were compared with tamoxifen, an antiestrogen, by monitoring rat estrous cycling. Four-week supplementation of a high-fat diet with flaxseed (2.5, 5, or 10) or SDG (0.75, 1.5 or 3.0 mg/day) produced a dose-related cessation or lengthening (by 18-39) of estrous cycles in up to 66 of rats. With tamoxifen (1 mg/kg body wt./day), 83 of the animals had irregular cycles or were in persistent diestrus. Flaxseed and SDG were antiestrogenic without gross tissue toxicity.

#### **Bibliographic Information**

**Phytochemicals: biochemical markers of ingestion, absorption and metabolism using flaxseed as a model.** Hasler, Clare M. 103 Agricultural Bioprocess Lab, Functional Foods for Health Program, Department of Food Science and Human Nutrition, Urbana, IL, USA. Editor(s): Lachance, Paul A. *Nutraceuticals: Designer Foods III: Garlic, Soy and Licorice*, [Course on Designer Foods, Proceedings], 3rd, Washington, D. C., May 23-25, 1994 (1997), 39-43. Publisher: Food & Nutrition Press, Trumbull, Conn CODEN: 65EOA3 Conference; General Review written in English. CAN 127:345613 AN 1997:695918 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

#### **Abstract**

A review with 19 refs. Phytochems. will play an increasingly important role in optimal nutrition in the future. Flaxseed is the richest source of a unique class of phytochems. - the mammalian lignans; enterodiol and enterolactone. Lignans are significantly elevated in human urine following flaxseed consumption, and are thought to have potential as a chemopreventive agent because of their ability to modulate estrogen metab. Flaxseed may serve as a model to examine the ingestion, absorption and metab. of phytochems. Reliable markers of phytochem. metab. are necessary to ascertain the safety and efficacy of addnl. designer/functional foods as this new field in the food and nutrition sciences continues to develop.

#### **Bibliographic Information**

**Chemical studies of phytoestrogens and related compounds in dietary supplements: flax and chaparral.** Obermeyer, W. R.; Musser, S. M.; Betz, J. M.; Casey, R. E.; Pohland, A. E.; Page, S. W. Center Food Safety Applied Nutrition, Food and Drug Administration, Washington, DC, USA. *Proceedings of the Society for Experimental Biology and Medicine* (1995), 208(1), 6-12. Publisher: Blackwell, CODEN: PSEBAA ISSN: 0037-9727. Journal written in English. CAN 122:159128 AN 1995:293252 CAPLUS (Copyright (C) 2005 ACS on SciFinder (R))

#### **Abstract**

HPLC and mass spectrometric (MS) procedures were developed to det. lignans in flaxseed (*Linum usitatissimum*) and chaparral (*Larrea tridentata*). Flaxseed contains high levels of phytoestrogens. Chaparral has been assocd. with acute nonviral toxic hepatitis and contains lignans that are structurally similar to known estrogenic compds. Both flaxseed and chaparral products have been marketed as dietary supplements. A mild enzyme hydrolysis procedure to prevent the formation of artifacts in the isolation step was used in the detn. of secoisolariciresinol in flaxseed products. HPLC with UV spectral or MS detection was used as the determinative steps. HPLC procedures with UV detection and mass spectrometry were developed to characterize the phenolic components, including lignans and flavonoids, of chaparral and to direct fractionation studies for the bioassays.