

Hygeia:: journal for drugs and medicines

October2012-March 2013

OPEN ACCESS

A half yearly scientific, international, open access journal for drugs and medicines

Research article section: Pharmacology/Natural products



Pharmacological properties of Flax seeds: A Review

Nirmala Halligudi

Pharmacy Department, Oman Medical College, Muscat, Sultanate of Oman.

Article history: Received: 30 June 2012, revised: 14 July, 2012, accepted: 16 August 2012, Available online: 10 October 2012

Abstract

Plan: To review on the pharmacological potential of flax seeds

Prologue: Flax oil and flax seeds are being rediscovered as true health foods. They definitely merit being included on any top-ten list of foods that are good for life. Flax is not a new food. It is actually one of the older and, perhaps, one of the original "health foods," treasured because of its healing properties throughout the Roman Empire. Flax was one of the original "medicines" used by Hippocrates. Flax could be dubbed the "forgotten oil." It has fallen out of favor because oil manufacturers have found nutritious oils to be less profitable.

Outcome: The very nutrients that give flax its nutritional benefits - essential fatty acids - also give it a short shelf life, making it more expensive to produce, transport, and store. Besides being the best source of omega 3's, flax oil is a good source of omega 6, or linoleic acid (LA). Sunflower, safflower, and sesame oil are greater sources of omega 6 fatty acids but they don't contain any omega-3 fatty acids. Flax oil is 45 to 60 percent the omega-3 fatty acid alpha-linolenic acid (ALA). In addition to nutritious fats, flax seeds contain other nutrients which make eating the whole seed superior to consuming just the extracted oil.

Key words: Flax seed, antioxidant, cardiovascular activity, anti cancer, Pharmacological activity

1. Introduction

Linum usitatissimum (Linn.), commonly known as flaxseed or linseed belongs to the family Linaceae. The flax plant is not a new crop and is native to West Asia and the Mediterranean. As the source of linen fiber, flax has been cultivated since at least 5000 BC (Oomah, 2001). Traditionally, flaxseed has been grown for its oil. Flaxseed has been playing a major role in the field of diet and disease research due to its potential health benefits associated with high content of α -linolenic acid (ALA)(57%), which is an essential omega-3-fatty acid and also because of a major lignan, namely secoisolariciresinoldiglucoside (SDG). Flaxseed is an oilseed that contains about 38–45% oil. ALA content in flax oil is 55–60% and lignan content in flaxseed is up to 13 mg/g flaxseed (Hallet *al.*, 2006). The lignan SDG is converted by bacteria in the colon of humans and other animals to enterodiol and enterolactone, referred to as mammalian lignans.



For Correspondence:

drnirma@yahoo.co.in

Contact: 00968-92348200

Hygeia.J.D.Med. Vol.4 (2), Oct. 2012

© 2012, Hygeia journal for drugs and medicines, all rights reserved. 2229 3590, 0975 6221

Nirmala Halligudi

These exhibit weak estrogenic activity as they can bind to estrogen receptors on cell membranes (Nesbitt *et al.*, 1999). The interest in ALA and lignans has opened opportunities^[1].

Flax, Linseed (French: *Lin*; German: *Flachs*; Spanish: *Lino*; Italian: *Lino*; Portuguese: *Linho*) Flax, common name for a family of plants, and for plants of a genus within that family. One species (*Linum usitatissimum*) is grown extensively for its fiber and seed. Other species are cultivated as ornamental plants or for pharmaceuticals. Flax plants range in height from 30 to 100 cm (12 to 40 in) and have narrow, alternate, lance like leaves. The flowers of most cultivated varieties range in color from deep to pale shades of blue. Some garden varieties have white, violet, pink, or red blossoms^[2].

Flaxseed is also an good source of protein and dietary fibre, accounting for 20% and 28% of the flax seed, respectively (Hall *et al.*, 2006) Flaxseed has gained much importance in recent times as ethno medicine due to its wide pharmacological actions. Although its therapeutic potential, as antioxidant, primarily as hydroxyl radical scavenger, anticancer, antidiabetic antiviral, bactericidal, anti-inflammatory, and ant atherosclerotic agent is known (Zanwar *et al.*,2010; Rajesha *et al.*, 2006; Chen *et al.*, 2002; Prasad, 2000;Collins *et al.*, 2003; Kinniry *et al.*, 2006; Prasad, 1997),very few studies evaluating its cardio protective potential are presently available (Penumathsa *et al.*, 2008, 2007).

Flax, linseed^[2]



Common name: Flax *Latin name:* *Linum usitatissimum*, Synonyms: Linseed, Common Flax, Flax Weed, Lint Bells, and Toad Flax *Family:* Linaceae *Habitat:* The plant is native to the temperate regions of Europe and Asia. *Description:* Flax is a small, herbaceous, annual plant, growing to 1, 2 meters tall. It has erect, smooth stem and glaucous green, linear leaves.

Flowers are small, five-petalled, pale blue or bright red in color. Fruits are round, dry capsules filled with brown seeds. Parts used: Seed,

Useful components: Fixed oil, mucilage, proteins, linamarin, omega-3 fatty Acids, Medicinal **use:** Flax seeds are considered to be extremely beneficial for different types of ailments. Used internally, the seeds are very useful in treatment of constipation and elimination of secretions in the respiratory tract. They are helpful in cases of bronchitis and colds. Daily use of flax oil protects gastric and urinary membrane. It is also said that Flax seeds can act as a helpful prevention against angina pectoris and arteriosclerosis. They can also be helpful in reducing the cholesterol levels. Taken externally, the oil obtained from the seeds is recognized due to its demulcent and emollient properties. It protects and softens the irritated skin.

Safety: Excessive use of Flax seeds with inadequate water can lead to bowel obstruction. Some herbs could react with certain medication. Therefore, it is advisable to consult your doctor before consumption of any herb.

A. Traditional Medicinal Uses

Flaxseed as a Poultice for Boils and Skin Abscesses

Roll about 3 tbs. of flaxseed in a 6-inch square of clean, white cloth. Twist either end tightly to contain the flaxseed. Holding the flax parcel by each of its two ends; dip the middle portion into a small bowl of boiling water. Wring it out, and place the poultice on the infected area. Cover it with a dry cloth. The flaxseed retains the heat, providing relief to the infected area. Remove the poultice when it has cooled.^[2]

Flaxseed, or linseed, is an ancient grain that may have originated in Egypt. The seeds, oil and seed meal can be used in many ways. Flaxseeds contain phytoestrogens, which may reduce your risk of breast cancer and possibly prevent a recurrence. The fibers from the flax plant have been used in linen fabric, yarns and bandages.

Flax as a Gel for Hair: An Albertan says that when she was young, women used to boil flaxseed in water and then use the liquid as a setting gel for their hair. It apparently worked very well!

B. Components of flax seed:

Alpha-linolenic acid (ALA), cyanogenic glycosides (linamarin, linustatin, neolinustin), unsaturated fatty acids (linolenic acid, linoleic acid, oleic acid), soluble flaxseed fiber mucilage (d-Xylose, L-Galactose, L-Rhamnose, d-galacturonic acid), lignans (secoisolariciresinol diglycoside (SDG)), monoglycerides, triglycerides, free sterols, sterol esters, hydrocarbons (protein), balast, phenylpropane derivatives.

Components of flaxseed oil:

Alpha-linolenic acid (ALA), unsaturated fatty acids (linolenic acid, linoleic acid, and oleic acid).

C. Components of flax root:

The roots of *L. usitatissimum* contain measurable concentrations of lignans and isoflavones.^[3]

Overview:

Flaxseed is composed of multiple chemical constituents, the mechanisms of which have not been fully elucidated. Studies have attributed different properties to the plant, seed, oil, and individual plant components. The biological activity of flax lignans is often attributed to their conversion to the mammalian lignans enterolactone and enterodiol.^[4] However, intermediate compounds generated during the digestion and metabolism of flax lignans, such as secoisolariciresinol diglycoside (SDG) and its aglycones and secoisolariciresinol (Seco), may also be the principal bioactive molecule. The plant, seed, and oil contain polyunsaturated fatty acids (PUFA), including alpha-linolenic acid (ALA) and linoleic acid. ALA is poorly converted by the human body to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in certain populations that lack the enzymatic capacity to do this conversion.^[5]

Nirmala Halligudi

Flaxseed also contains monounsaturated fatty acids (MUFAs), such as oleic acid. ALA and linoleic acid are both essential fatty acids (EFA), meaning they cannot be synthesized by the human body and must be derived from the diet.^[6,7,8] ALA is a precursor to EPA^[9,10], and ingestion of flaxseed has been shown to increase cellular EPA levels in a linear manner^[10,11]. However, the linoleic component of flaxseed (an omega-6 fatty acid) is reportedly capable of antagonizing the conversion of ALA to EPA.^[10] Flaxseed is a concentrated food source of the lignan SDG. Flaxseed also contains small quantities of the lignan matairesinol.^[12] SDG and matairesinol can be converted into mammalian lignans such as enterodiol and enterolactone by colonic bacteria.^[12,13]

D. Health-promoting properties of flax

Flax oil, flax seeds, and the omega-3 fatty acids they contain are good for your health. Here are some of the ways flax helps your body.

1. Flax promotes cardiovascular health. The ultra-high levels of omega-3 fatty acids lower LDL (bad) cholesterol levels. Fish oils and algae are also good sources of essential fatty acids.
2. Flax promotes colon health. It has anti-cancer properties and, as a natural lubricant and a rich fiber source, it lowers the risk of constipation.
3. Flax supplements can boost immunity. One study showed that school children supplemented with less than a teaspoon of flax oil a day had fewer and less severe respiratory infections than children not supplemented with flax oil.
4. Flax provides fats that are precursors for brain building. This is especially important at the stage of life when a child's brain grows the fastest, in uterus and during infancy. A prudent mom should consider supplementing her diet with a daily tablespoon of flax oil during her pregnancy and while breastfeeding.
5. Flax promotes healthy skin. I have used flax oil as a dietary supplement in my patients who seem to have dry skin or eczema, or whose skin is particularly sun-sensitive.
6. Flax may lessen the severity of diabetes by stabilizing blood-sugar levels.
7. Flax fat can be slimming. Fats high in essential fatty acids, such as flax, increase the body's metabolic rate, helping to burn the excess, unhealthy fats in the body. Eating the right kind of fat gives you a better fighting chance of your body storing the right amount of fats. This is called thermogenesis, a process in which specialized fat cells throughout the body (called brown fat) click into high gear and burn more fat when activated by essential fatty acids, especially gamma-linolenic acid (GLA).

Comparison of Brown and Yellow Flax

Brown and yellow (Omega) varieties of flax are virtually identical in their nutrient content as shown in Table 1. The nutritional differences between them are small and likely result from differences in growing conditions. As mentioned previously, seed coat color is determined by the amount of pigment present, a feature that can be changed through normal plant breeding practices.

Consumers can buy brown or yellow flax based on price and appearance of the flax containing food product, since the nutritional value of brown and yellow flax is similar^[14]

Table 1 comparison of brown flax and yellow flax

Constituent	Brown flax	Yellow flax
g/100 g		
Protein (% nitrogen x 6.25)	22.3	29.2
Oil/fat	44.4	43.6
% of total fatty acids		
Specific fatty acids		
Saturated fatty acids	8.7	9.0
Monounsaturated fatty acids	18.0	23.5
Polyunsaturated fatty acids		
Alpha-linolenic acid	58.2	50.9
Linoleic acid	14.6	15.8

The epidemiological, clinical and laboratory data have shown that flax seeds contains many bioactive products which are beneficial to human in general. Although additional studies are warranted in humans, compelling evidence supports the health effects and its implications in preventing or reducing the risk of cardiovascular ailments, strokes, diabetics' and cancer

- *Antiarrhythmic effects:*

Limited human study and scientific reviews suggest a possible antiarrhythmic effect of ALA and omega-3 fatty acids.^[16,17,18] However, another study found that antiarrhythmic effects were concentration-dependently enhanced by DHA and EPA, but not by ALA.^[19] Higher intake of dietary linolenic acid might be associated with a reduced risk of abnormally prolonged repolarization in men and women.^[20]

- *Anticoagulant and antiplatelet effects:*

Available data specific to flaxseed (which is unique from fish oil in that it contains up to 20% omega-6 fatty acids and its omega-3 fatty acids must be converted into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) are conflicting regarding its effects on platelet function. Two studies comparing flaxseed oil to a linoleic acid control (one study in healthy volunteers (N=11) and one study in patients with rheumatoid arthritis (N=22)) reported that flaxseed oil decreased collagen-stimulated platelet aggregation and bleeding time.^[21,22] Use of a flaxseed supplement also decreased thrombin-stimulated platelet aggregation.^[23] Conversely, a crossover study in which 10 healthy volunteers consumed both a standardized diet with no supplementation and one supplemented with flaxseed oil found that flaxseed oil had no effect on bleeding time, prothrombin time, or partial thromboplastin time.^[24]

There are case reports of possible interactions between fish oil and warfarin/aspirin^[25,26], though a recent review concludes that available clinical data do not support the existence of any such clinically relevant interaction^[27].

- *Antidiabetic effects:*

Flax has been studied for its effects on blood sugar, but reports are inconclusive. In a case series, postprandial glucose was reduced by 27% following meals with flaxseed.^[28] In a case series including 15 obese patients, Nestel et al. reported that a four-week diet high in alpha-linolenic acid (ALA) (20g from margarine products based on flax oil) diminished insulin sensitivity.^[29] In men with type 2 diabetes, ingestion of omega-3 fatty acids (not specific to flax) showed increases in fasting glucose levels and a 22% increase in mixed meal glucose levels.^[30]

- *Antilipemic effects:*

Proposed lipid-lowering effects of flaxseed (not flaxseed oil) have been attributed to the fiber component consisting of d-xylose, l-galactose, l-rhamnose, d-galacturonic acid, and galactose.^[31] It has been reported that defatted flaxseed (equivalent to the fiber component of flaxseed) can significantly reduce levels of total cholesterol and low-density lipoproteins (LDL)⁷, and triglycerides^[32]. The fiber portion of flaxseed has been proposed to exert lipid-lowering effects by enhancing gastric emptying time, altering transit time, interfering with bulk-phase diffusion of fat and increasing excretion of bile acids. It is thought that flaxseed may exert a beneficial effect on atherosclerotic plaque formation due to the antioxidant properties of lignans.^[33] The results of a mouse study suggest that the lipid lowering effect of flax is not hepatic mediated and may be at the level of cholesterol absorption and/or bile acid reabsorption.^[34]

- *Antineoplastic effects:*

In 2005, flaxseed was one of the most commonly used products for treating breast cancer.^[35] Flaxseed contains the highest amount of plant lignans and flaxseed and its defatted meal are the highest producers of mammalian lignans enterolactone and enterodiol (mean 60,110 ± 7,431) compared to other oilseeds, legume hulls, seaweeds and cereal brans.^[36] The amount of lignan production in processed foods is generally linearly dependent on the percent of flaxseed in the product.^[37] Furthermore, several researchers noted that the breast cancer-modulating effects of phytoestrogens are dependent both on the background diet, genetic makeup, and on the timing of exposure in the life cycle.^[38-39] The lignan components of flaxseed are often attributed as the protection against hormone-sensitive cancers via antagonizing estrogen receptors or inhibiting enzymes involved with the synthesis of sex hormones^[12,40], or via effects on epidermal growth factor receptors^[41,42] Feeding flaxseed, purified flaxseed lignan or oil to carcinogen treated rats have been shown to be protective against colon cancer.^[43,44,45,46,47]

- *Hormonal effects:*

Flaxseed (not flaxseed oil) is a rich source of plant lignans.^[48,49] Lignans are often referred to as phytoestrogens, and may possess estrogen receptor agonist or antagonist properties, with unclear effects on hormone-sensitive cancers such as breast, uterine, and prostate cancer.^[40] It has been proposed that flaxseed and its lignans have potent antiestrogenic effects on estrogen receptor-positive breast cancer.^[50] Flaxseed is a concentrated food source of the lignan secoisolariciresinol diglycoside (SDG).^[12]

Enterolactone and enterodiol (metabolized from flaxseed in the bowel) may decrease cell proliferation and inhibit aromatase, 5-alpha-reductase, and 17-beta-hydroxysteroid dehydrogenase activity, which may offer a reduction in the risk of breast, prostate and other hormone sensitive cancers.^[12] It has also been shown that lignans increase sex-hormone-binding globulin synthesis.^[12] In humans, flaxseed has been reported to significantly reduce serum levels of 17-beta-estradiol and estrone sulfate and increase prolactin levels^[12], increase the urinary ratio of the two estrogen metabolites 2-hydroxyestrogen and 16 alpha-hydroxyestrone^[51,52], increase urinary excretion levels of enterodiol and enterolactone^[53] and increase fecal excretion of enterodiol, enterolactone, and matairesinol.^[54] It has been suggested that flaxseed has more potent effects on estrogen metabolism than soy.^[55]

References

1. Anand A. Zanwar Mahabaleshwar V. Hegde, Subhash L. Bodhankar *Interdiscip Toxicol.* **2011** June; 4(2): 90–97
2. Q LIFE Health & Beautyproducts: Flaxseed (Linseed) *Properties and Benefits* www.frontiernet.net/~batory/properties.html
3. Abarzua, S., Szewczyk, M., Gailus, S., Richter, D. U., Ruth, W., Briese, V., and Piechulla, B. Effects of phytoestrogen extracts from *Linum usitatissimum* on the Jeg3 human trophoblast tumour cell line. *Anticancer Res* **2007**;27(4A):2053-2058.
4. Muir, A. D. Flax lignans--analytical methods and how they influence our understanding of biological activity. *J AOAC Int* **2006**;89(4):1147-1157.
5. Damude, H. G. and Kinney, A. J. Engineering oilseed plants for a sustainable, land-based source of long chain polyunsaturated fatty acids. *Lipids* **2007**;42(3):179-185.
6. Dyerberg, J. Linolenate-derived polyunsaturated fatty acids and prevention of atherosclerosis. *Nutr Rev* **1986**;44(4):125-134.
7. Siguel, E. N. Essential and trans fatty acid metabolism in health and disease. *Compr Ther* **1994**;20(9):500-510.
8. Stoll, A. L., Locke, C. A., Marangell, L. B., and Severus, W. E. Omega-3 fatty acids and bipolar disorder: a review. *Prostaglandins Leukot Essent Fatty Acids* **1999**;60(5-6):329-337.
9. Mantzioris, E., James, M. J., Gibson, R. A., and Cleland, L. G. Nutritional attributes of dietary flaxseed oil. *Am J Clin Nutr* **1995**;62(4):841.
10. Mantzioris, E., James, M. J., Gibson, R. A., and Cleland, L. G. Differences exist in the relationships between dietary linoleic and alpha-linolenic acids and their respective long-chain metabolites. *Am J Clin Nutr* **1995**;61(2):320-324.
11. Mantzioris, E., James, M. J., Gibson, R. A., and Cleland, L. G. Dietary substitution with an alpha-linolenic acid-rich vegetable oil increases eicosapentaenoic acid concentrations in tissues. *Am J Clin Nutr* **1994**;59(6):1304-1309.
12. Hutchins, A. M., Martini, M. C., Olson, B. A., Thomas, W., and Slavin, J. L. Flaxseed consumption influences endogenous hormone concentrations in postmenopausal women. *Nutr Cancer* **2001**;39(1):58-65.
13. Rickard, S. E., Orcheson, L. J., Seidl, M. M., Luyengi, L., Fong, H. H., and Thompson, L. U. Dose-dependent production of mammalian lignans in rats and in vitro from the purified precursor secoisolariciresinol diglycoside in flaxseed. *J Nutr* **1996**;126(8):2012-2019.
14. www.flaxcouncil.ca/english/pdf/FlxPrmr_4ed_Chpt1.pdf
15. Pam Stephan, *About.com Guide 21, 2012*
16. Christensen, J. H., Schmidt, E. B., Molenberg, D., and Toft, E. Alpha-linolenic acid and heart rate variability in women examined for coronary artery disease. *Nutr Metab Cardiovasc Dis* **2005**;15(5):345-351.
17. Matthan, N. R., Jordan, H., Chung, M., Lichtenstein, A. H., Lathrop, D. A., and Lau, J. A systematic review and meta-analysis of the impact of omega-3 fatty acids on selected arrhythmia outcomes in animal models. *Metabolism* **2005**;54(12):1557-1565.
18. Mozaffarian, D. Does alpha-linolenic acid intake reduce the risk of coronary heart disease? A review of the evidence. *Altern Ther Health Med* **2005**;11(3):24-30.
19. Dhein, S., Michaelis, B., and Mohr, F. W. Antiarrhythmic and electrophysiological effects of long-chain omega-3 polyunsaturated fatty acids. *Naunyn Schmiedebergs Arch Pharmacol* **2005**;371(3):202-211.
20. Djousse, L., Rautaharju, P. M., Hopkins, P. N., Whitsel, E. A., Arnett, D. K., Eckfeldt, J. H., Province, M. A., and Ellison, R. C. Dietary linolenic acid and adjusted QT and JT intervals in the National Heart, Lung, and Blood Institute Family Heart study. *J Am Coll Cardiol* **5-17-2005**;45(10):1716-1722.

21. Allman, M. A., Pena, M. M., and Pang, D. Supplementation with flaxseed oil versus sunflowerseed oil in healthy young men consuming a low fat diet: effects on platelet composition and function. *Eur J Clin Nutr* **1995**;49(3):169-178.
22. Nordstrom, D. C., Honkanen, V. E., Nasu, Y., Antila, E., Friman, C., and Kontinen, Y. T. Alpha-linolenic acid in the treatment of rheumatoid arthritis. A double-blind, placebo-controlled and randomized study: flaxseed vs. safflower seed. *Rheumatol Int* **1995**;14(6):231-234.
23. Bierenbaum ML, Reichstein R, Watkins TR, and et al. Reducing atherogenic risk in hyperlipemic humans with flax seed supplementation: a preliminary report. *J Am Coll Nutr* **1993**;12:501-504.
24. Kelley, D. S., Nelson, G. J., Love, J. E., Branch, L. B., Taylor, P. C., Schmidt, P. C., Mackey, B. E., and Iacono, J. M. Dietary alpha-linolenic acid alters tissue fatty acid composition, but not blood lipids, lipoproteins or coagulation status in humans. *Lipids* **1993**;28(6):533-537.
25. Buckley, M. S., Goff, A. D., and Knapp, W. E. Fish oil interaction with warfarin. *Ann Pharmacother* **2004**;38(1):50-52.
26. McClaskey, E. M., and Michalets, E. L. Subdural hematoma after a fall in an elderly patient taking high-dose omega-3 fatty acids with warfarin and aspirin: case report and review of the literature. *Pharmacotherapy* **2007**;27(1):152-160.
27. Bays, H. E. Safety considerations with omega-3 fatty acid therapy. *Am J Cardiol* 3-19-**2007**;99(6A):35C-43C.
28. Cunnane, S. C., Ganguli, S., Menard, C., Liede, A. C., Hamadeh, M. J., Chen, Z. Y., Wolever, T. M., and Jenkins, D. J. High alpha-linolenic acid flaxseed (*Linum usitatissimum*): some nutritional properties in humans. *Br J Nutr* **1993**;69(2):443-453.
29. Nestel, P. J., Pomeroy, S. E., Sasahara, T., Yamashita, T., Liang, Y. L., Dart, A. M., Jennings, G. L., Abbey, M., and Cameron, J. D. Arterial compliance in obese subjects is improved with dietary plant n-3 fatty acid from flaxseed oil despite increased LDL oxidizability. *Arterioscler Thromb Vasc Biol* **1997**;17(6):1163-1170.
30. Glauber, H., Wallace, P., Griver, K., and Brechtel, G. Adverse metabolic effect of omega-3 fatty acids in non-insulin- dependent diabetes mellitus. *Ann Intern Med* **1988**;108(5):663-668.
31. Jenkins, D. J., Kendall, C. W., Vidgen, E., Agarwal, S., Rao, A. V., Rosenberg, R. S., Diamandis, E. P., Novokmet, R., Mehling, C. C., Perera, T., Griffin, L. C., and Cunnane, S. C. Health aspects of partially defatted flaxseed, including effects on serum lipids, oxidative measures, and ex vivo androgen and progestin activity: a controlled crossover trial. *Am J Clin Nutr* **1999**;69(3):395-402.
32. Bhatena, S. J., Ali, A. A., Haudenschild, C., Latham, P., Ranich, T., Mohamed, A. I., Hansen, C. T., and Velasquez, M. T. Dietary flaxseed meal is more protective than soy protein concentrate against hypertriglyceridemia and steatosis of the liver in an animal model of obesity. *J Am Coll Nutr* **2003**;22(2):157-164.
33. Prasad, K. Dietary flax seed in prevention of hypercholesterolemic atherosclerosis. *Atherosclerosis* 7-11-**1997**;132(1):69-76.
34. Pellizzon, M. A., Billheimer, J. T., Bloedon, L. T., Szapary, P. O., and Rader, D. J. Flaxseed reduces plasma cholesterol levels in hypercholesterolemic mouse models. *J Am Coll Nutr* **2007**;26(1):66-75.
35. Boon, H. S., Olatunde, F., and Zick, S. M. Trends in complementary/alternative medicine use by breast cancer survivors: comparing survey data from 1998 and 2005. *BMC Womens Health* **2007**;7:4.
36. Thompson, L. U., Robb, P., Serraino, M., and Cheung, F. Mammalian lignan production from various foods. *Nutr Cancer* **1991**;16(1):43-52.
37. Nesbitt, P. D. and Thompson, L. U. Lignans in homemade and commercial products containing flaxseed. *Nutr Cancer* **1997**;29(3):222-227.
38. Luijten, M., Thomsen, A. R., van den Berg, J. A., Wester, P. W., Verhoef, A., Nagelkerke, N. J., Adlercreutz, H., van Kranen, H. J., Piersma, A. H., Sorensen, I. K., Rao, G. N., and van Kreijl, C. F. Effects of soy-derived isoflavones and a high-fat diet on spontaneous mammary tumor development in Tg.NK (MMTV/c-neu) mice. *Nutr Cancer* **2004**;50(1):46-54.
39. McCann, S. E., Wactawski-Wende, J., Kufel, K., Olson, J., Ovando, B., Kadlubar, S. N., Davis, W., Carter, L., Muti, P., Shields, P. G., and Freudenheim, J. L. Changes in 2-hydroxysterone and 16alpha-hydroxysterone metabolism with flaxseed consumption: modification by COMT and CYP1B1 genotype. *Cancer Epidemiol Biomarkers Prev* **2007**;16(2):256-262.
40. Adlercreutz, H. Epidemiology of phytoestrogens. *Baillieres Clin Endocrinol Metab* **1998**;12(4):605-623.
41. Chen, J., Stavro, P. M., and Thompson, L. U. Dietary flaxseed inhibits human breast cancer growth and metastasis and downregulates expression of insulin-like growth factor and epidermal growth factor receptor. *Nutr Cancer* **2002**;43(2):187-192.
42. Dabrosin, C., Chen, J., Wang, L., and Thompson, L. U. Flaxseed inhibits metastasis and decreases extracellular vascular endothelial growth factor in human breast cancer xenografts. *Cancer Lett* 11-8-**2002**;185(1):31-37.
43. Bommareddy, A., Arasada, B. L., Mathees, D. P., and Dwivedi, C. Chemopreventive effects of dietary flaxseed on colon tumor development. *Nutr Cancer* **2006**;54(2):216-222.
44. Dwivedi, C., Natarajan, K., and Mathees, D. P. Chemopreventive effects of dietary flaxseed oil on colon tumor development. *Nutr Cancer* **2005**;51(1):52-58.
45. Jenab, M. and Thompson, L. U. The influence of flaxseed and lignans on colon carcinogenesis and beta- glucuronidase activity. *Carcinogenesis* **1996**;17(6):1343-1348.
46. Serraino, M. and Thompson, L. U. Flaxseed supplementation and early markers of colon carcinogenesis. *Cancer Lett* 4-15-**1992**;63(2):159-165.
47. Williams, D., Verghese, M., Walker, L. T., Boateng, J., Shackelford, L., and Chawan, C. B. Flax seed oil and flax seed meal reduce the formation of aberrant crypt foci (ACF) in azoxymethane-induced colon cancer in Fisher 344 male rats. *Food Chem Toxicol* **2007**;45(1):153-159.
48. Prasad, K., Mantha, S. V., Muir, A. D., and Westcott, N. D. Reduction of hypercholesterolemic atherosclerosis by CDC-flaxseed with very low alpha-linolenic acid. *Atherosclerosis* **1998**;136(2):367-375.
49. Prasad, K. Reduction of serum cholesterol and hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinol diglucoside isolated from flaxseed. *Circulation* 3-16-**1999**;99(10):1355-1362.
50. Bergman Jungstrom, M., Thompson, L. U., and Dabrosin, C. Flaxseed and its lignans inhibit estradiol-induced growth, angiogenesis, and secretion of vascular endothelial growth factor in human breast cancer xenografts in vivo. *Clin Cancer Res* 2-1-**2007**;13(3):1061-1067.
51. Haggans, C. J., Travelli, E. J., Thomas, W., Martini, M. C., and Slavin, J. L. The effect of flaxseed and wheat bran consumption on urinary estrogen metabolites in premenopausal women. *Cancer Epidemiol Biomarkers Prev* **2000**;9(7):719-725.
52. Haggans, C. J., Hutchins, A. M., Olson, B. A., Thomas, W., Martini, M. C., and Slavin, J. L. Effect of flaxseed consumption on urinary estrogen metabolites in postmenopausal women. *Nutr Cancer* **1999**;33(2):188-195.
53. Shultz, TD, Bonorden, WR, and Seaman, WR. Effects of short-term flaxseed consumption on lignan and sex hormone metabolism. *Nutr Res* **1991**;11:1089-1100.
54. Kurzer, M. S., Lampe, J. W., Martini, M. C., and Adlercreutz, H. Fecal lignan and isoflavonoid excretion in premenopausal women consuming flaxseed powder. *Cancer Epidemiol Biomarkers Prev* **1995**;4(4):353-358.
55. Brooks, J. D., Ward, W. E., Lewis, J. E., Hilditch, J., Nickell, L., Wong, E., and Thompson, L. U. Supplementation with flaxseed alters estrogen metabolism in postmenopausal women to a greater extent than does supplementation with an equal amount of soy. *Am J Clin Nutr* **2004**;79(2):318-325.