Flax

Linum usitatissimum L.

[Fam. *Linaceae*]

Overview

The crude form of flax is the dried, ripe seed of all varieties of *Linum usitatissimum* L. [Fam. *Linaceae*]. Commercial preparations include ground seed, gruel, and expressed oil. The oil is marketed in bottles or in soft-gel capsules. The seeds can be consumed raw or in baked foods. Flax has become popular in the mainstream market in many forms, including raw seeds, expressed oils, and as an ingredient in breads, muffins, cereals, and breakfast bars. It is estimated that 80% of Americans are deficient in the omega-3 essential fatty acids which flax provides. Flax oil contains 50–60% alpha-linolenic acid. Flax is also one of the most concentrated sources of lignans (phenolic resins found in many plants), containing 100 to 800 times the amount found in other foods.

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Primary Uses

Internal

- Hyperlipidemia
- Atherosclerosis
- Breast cancer (may reduce risk of breast cancer and metastasis)
- Chronic constipation
- Colon damage by laxative abuse
- Irritable colon
- Diverticulitis
- Gastritis and enteritis

External

- Inflammation, local, as a poultice

Other Potential Uses

- Lupus nephritis
- Osteoporosis (reduction of resorption rate)
- Prostate cancer (may reduce hormone and cell proliferation levels, may increase apoptosis)
- Rheumatoid arthritis

Pharmacological Actions

CRUDE PREPARATIONS: Laxative.

GROUND FLAX OR OIL PREPARATIONS: Develops brain function; lowers LDL serum cholesterol; antiplatelet aggregation; anti-inflammatory; antimetastatic; reduces proteinuria; increases creatinine clearance; reduces glomerulosclerosis.

Dosage and Administration

Internal

CRUDE PREPARATIONS: Flax can be used continuously as a nutritional source, or as a bulk laxative.

BRUISED OR WHOLE SEED: 1 tablespoon (5 g) of whole, "bruised," or ground seed soaked in water and taken with a glassful of liquid 3 times daily. Grind the seeds to improve absorption of phytochemicals for therapeutic efficacy.

MUCILAGE (GRUEL): Soak 2–3 tablespoons of milled flaxseed in 200–300 ml water, strain after 30 minutes.

OIL: 1–2 tablespoons daily.

FLAX OIL CAPSULES: 3–6 capsules containing 1,000 mg each oil for general health maintenance.

GROUND SEED: 2.5 teaspoons, 2–3 times daily.

External

CATAPLASM (POULTICE): Semisolid paste containing 30–50 g flaxseed flour for a moist-heat direct application to the skin, used like a poultice as a counter-irritant. Draws blood to the surface to remove deep-seated inflammation. Flaxseed meal is traditionally mixed with mustard seed powder in this application.

COMPRESS OR FOMENTATION: A cloth is saturated with a hot, semisolid preparation containing 30–50 g flaxseed flour, folded, and applied firmly for a moist-heat direct application to the skin to relieve pain or inflammation.

NOTE: Flax oil and ground flaxseeds should be stored in air tight containers in a cool area away from direct sun light. Flax oil soft-gel capsules should be stored at room temperature in air tight bottles.

Contraindications

Consult with a healthcare provider in cases of ileus of any origin.

Pregnancy and Lactation: No known restrictions. Essential fatty acid (EFA) supplementation during pregnancy and nursing is beneficial for fetal and infant brain development and visual function.

Adverse Effects

None known at therapeutic dosages when directions are followed (i.e., consumption of adequate amounts of liquid 1:10).

Drug Interactions

As with any other mucilage, the whole or crushed seeds may inhibit the absorption of drugs or dietary nutrients. There are no known drug interactions for flax oil.

Clinical Review

In 18 clinical studies on flax that included a total of 90,648 participants, all but two demonstrated positive effects for cardiovascular health, breast cancer, prostate cancer, lupus, and arthritis. One randomized, double-blind, placebo-controlled (R, DB, PC) study performed on 22 participants using flaxseed oil concluded that the duration of supplementation may have been too short to have an effect on rheumatoid arthritis or that missing co-factors may have interfered with the clinical outcomes of this study. Two R, DB crossover trials found that flaxseed baked in food products produced a significant decrease in LDL cholesterol and in retarding the rate of bone resorption. In another investigation, consumption of flaxseed oil had no effect on glycemic control or insulin secretion. A R, PC, single-blind, crossover trial found partially defatted flaxseed baked in food products reduced LDL serum cholesterol levels to concentrations associated with ingestion of full-fat flaxseed. One study found secondary prevention of heart attack. Two epidemiological reports found a reduction in the incidence of breast cancer or metastasis in women who used flaxseed oil. A recent pilot study with flaxseed and low-fat diet showed possible benefits in reducing testosterone and cancer cell proliferation rates and increased apoptosis.

Flax

Linum usitatissimum L.
[Fam. *Linaceae*]

Overview

Flax has become popular in the mainstream market in many forms: raw seeds; expressed oils; and as an ingredient in breads, muffins, cereals, and breakfast bars. Flaxseed oil provides the beneficial essential fatty acids in which 80% of Americans are deficient. Flax oil contains 50–60% alpha-linolenic acid and is also one of the most concentrated sources of lignans (phenolic resins found in many plants), containing 100 to 800 times the amounts found in other foods.

Uses

Internal

Elevated lipid levels (e.g., high cholesterol); breast cancer (risk reduction); osteoporosis; lupus nephritis; rheumatoid arthritis, atherosclerosis; chronic constipation; irritable bowel and other colon disorders.

External

Local inflammation.

Dosage

Flax can be used long-term as a bulk laxative and as a nutritional supplement.

BRUISED OR WHOLE SEED: 1 tablespoon (5 g) of whole, "bruised," or ground seed soaked in water and taken with a glassful of liquid 3 times daily. Grinding the seeds improves absorption of plant nutrients.

MUCILAGE (GRUEL): Soak 2–3 tablespoons of milled flaxseed in 200–300 ml water, strain after 30 minutes.

OIL: 1–2 tablespoons daily.

FLAX OIL CAPSULES: 3–6 capsules containing 1,000 mg oil each for general health maintenance.

GROUND SEED: 2.5 teaspoons, 2–3 times daily.

COMPRESS OR FOMENTATION: Saturate cloth with a hot, semisolid preparation containing 30–50 g flaxseed flour. Fold and apply firmly for a moist-heat direct application to the skin to relieve pain or inflammation.

NOTE: Store flax oil and ground flaxseeds in air tight containers in a cool area away from direct sun light. Store flax oil soft-gel capsules at room temperature in air tight bottles.

Contraindications

Consult with a healthcare provider in cases of obstruction of bowels or painful, distended abdomen (ileus of any origin).

PREGNANCY AND LACTATION: There are no known restrictions for use during pregnancy or while breast-feeding.

Adverse Effects

There are no known adverse effects for individuals using flaxseed at the suggested dosages when directions are followed [e.g., take with plenty of liquids (1 part flaxseed to 10 parts liquid)].

Drug Interactions

Whole or crushed seeds produce a thick substance called mucilage which may affect the absorption of drugs or other nutrients taken simultaneously. There are no known drug interactions with flax oil.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

AMERICAN BOTANICAL COUNCIL

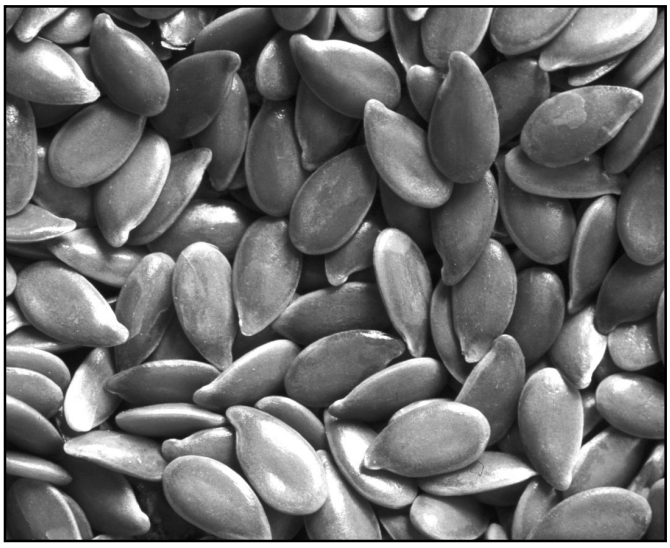
Flax

Linum usitatissimum L.

[Fam. *Linaceae*]

Overview

Flax has become popular in the mainstream market in many forms including raw seeds and expressed oils, and as an ingredient in breads, muffins, cereals, and breakfast bars (Blumenthal *et al.,* 2000). The oil from flaxseed, also called linseed, is one of the most concentrated plant sources of omega-3 fatty acids. It is also one of the most concentrated sources of lignans (phenolic resins found in many plants) containing 100–800 times the amount found in other foods (Mazur *et al.*, 1998; Mazur, 1998; Thompson *et al.*, 1991). Current research suggests that flax lignans are anti-atherogenic (Prasad, 1997), antioxidant, hypocholesterolemic, and anticarcinogenic (Nesbitt and Thompson, 1997). Flax, and some of its derivatives, is being studied for lowering LDL serum cholesterol, prevention of some cancers, and treatment of systemic lupus erythematosus (SLE). The largest flax producer is Canada (Haggerty, 1999). Flaxseed is an increasingly common ingredient in conventional foods, and is eaten either raw or in baked goods. Because phytochemicals (lignans and alpha-linolenic acid) from whole flaxseeds are poorly absorbed in the body, many people prefer to crush the seeds in order to obtain the optimal health benefit.



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Description

Flax preparations consist of the dried, ripe seed of all varieties of *Linum usitatissimum* L. [Fam. *Linaceae*] (Blumenthal *et al.,* 1998). The seeds can be consumed raw or in baked foods. Commercial preparations include ground seed, gruel, and expressed oil. The oil is marketed in bottles or in soft-gel capsules and contains 59% alpha-linolenic acid (ALA) (Bhatty, 1995).

Primary Uses

Internal

Cardiovascular

- Hyperlipidemia (Jenkins *et al.,* 1999; Arjmandi *et al.,* 1998a; Nestel *et al.*, 1997; Bierenbaum *et al.*, 1993; Cunnane *et al.,* 1995)
- Atherosclerosis (risk reduction) (Caughey *et al.,* 1996; Allman *et al.*, 1995; Bierenbaum *et al.*, 1993)

Breast Cancer

- May reduce risk of breast cancer and metastasis (Haggans *et al.*, 1999; Ingram *et al.*, 1997; Phipps *et al.*, 1993; Bougnoux *et al.*, 1994; Willett *et al.*, 1992)

Gastrointestinal

- Chronic constipation (Cunnane *et al.*, 1995; Blumenthal *et al.*, 1998)
- Colon damage by laxative abuse (Blumenthal *et al.*, 1998)
- Irritable colon (Blumenthal *et al.*, 1998)
- Diverticulitis (Blumenthal *et al.*, 1998)
- Gastritis and enteritis, as a mucilage (Blumenthal *et al.*, 1998)

Other Potential Uses

Internal

- Osteoporosis (reduction of resorption rate) (Arjmandi *et al.,* 1998b)
- Lupus nephritis (Clark *et al.*, 1995)
- Prostate cancer (may reduce hormone and cell proliferation levels, may increase apoptosis) (Demark-Wahnefried *et al.,* 2001)
- Rheumatoid arthritis (Nordstrom *et al.,* 1995; Caughey *et al.,* 1996)

External

- Inflammation, local, as a poultice (Blumenthal *et al.*, 1998)

Dosage

Internal

Crude Preparations

BRUISED OR WHOLE SEED: 1 tablespoon (5 g) of whole, "bruised", or ground seed, is soaked in water, and taken with a glassful of liquid 3 times daily. It is usually preferable to grind the seeds to improve the absorption of phytochemicals and the resulting therapeutic efficacy. NOTE: The effect typically begins 18–24 hours later (ESCOP, 1997).

MUCILAGE (GRUEL): 2–3 tablespoons of milled flaxseed are soaked in 200–300 ml water and strained after 30 minutes.

OIL: 1–2 tablespoons daily (Blumenthal *et al.*, 1998)

FLAX OIL CAPSULES: 3–6 capsules containing 1,000 mg each oil for general health maintenance.

External

Crude Preparations

CATAPLASM (POULTICE): Semisolid paste containing 30–50 g flaxseed flour for a moist-heat direct application to the skin, used like a poultice as a counter-irritant. Draws blood to the surface to remove deep-seated inflammation. NOTE: Flaxseed meal is traditionally mixed with mustard seed powder in this application.

COMPRESS OR FOMENTATION: Cloth saturated with a hot semi-solid preparation containing 30–50 g flaxseed flour. Folded and applied firmly for a moist-heat direct application to the skin to relieve pain or inflammation (Blumenthal *et al.*, 1998).

NOTE ABOUT PROPER STORAGE: Flax oil and ground flaxseeds must be stored in air tight containers in a cool area away from direct sun. Flax oil soft-gel capsules can be stored at room temperature in air tight bottles.

Duration of Administration

Internal

Crude Preparations (from flaxseeds)

Flax can be used continuously as a nutritional source (Bhatty, 1995), or as a bulk laxative.

Chemistry

Flaxseed contains 30–45% fixed oil, including triglycerides of alpha-linolenic, linoleic, oleic, stearic, palmitic, and myristic acids; 20–25% proteins; 3–10% mucilage, composed of neutral and acidic polysaccharides which, after hydrolysis, yield 8–10% galactose, 9–12% arabinose, 13–29% rhamnose, 25–27% xylose and galacturonic and about 30% mannuronic acids, sterols, and triterpenes (campesterol, stigmasterol, and sitosterol); 0.1–1.5% cyanogenic glycosides, mostly linustatin and neolinustatin and the monoglycosides linamarin and lotaustralin; and secoisolariciresinol diglucoside (SDG) (a precursor of lignans in mammals) (Bhatty, 1995; Budavari, 1996; ESCOP, 1997). A rapid RP-HPLC method was developed to quantify the lignan SDG in baked goods containing flaxseed or flax meal. Finely ground materials were found to have a significantly greater content of SDG than course materials (Muir and Westcott, 2000).

Pharmacological Actions

Crude Preparations

Laxative (Cunnane *et al.*, 1995; Blumenthal *et al.*, 1998).

Ground Flax or Oil Preparations

Human

Develops brain function (Simopoulos, 1991); lowers LDL serum cholesterol (Jenkins *et al.,* 1999; Arjmandi *et al.*, 1998a; Bierenbaum *et al.,* 1993); antiplatelet aggregation (Allman *et al.*, 1995; Bierenbaum *et al.*, 1993); anti-inflammatory (Caughey *et al.*, 1996); antimetastatic (Bougnoux *et al.*, 1994); reduces proteinuria; increases creatinine clearance; and reduces glomerulosclerosis (Clark *et al.*, 1995).

Animal

Develops neurotransmission, neuromusculation, and cognition (Walker, 1967; Lamptey *et al.*, 1976; Delion *et al.*, 1994, 1996; Frances *et al.,* 1995, 1996); may reduce breast and colon cancer risk (Serraino and Thompson, 1991, 1992a, 1992b; Jenab and Thompson, 1996); suppresses mammary tumor growth (Thompson *et al.*, 1996); prevents atherosclerosis (Prasad, 1997); regulates fertility and sperm quality (Kelso *et al.* 1997; Arya and Caglj, 1993).

In vitro

Anti-cancer in human breast, lung, and prostate cells, and in mouse myeloma cells (Begin *et al.*, 1986; Kumar and Das, 1995).

Mechanism of Action

- Stimulates bowels. Flax binds to water, mucilage swells, and stool volume increases (Weiss and Fintelmann, 2000; De Smet *et al*, 1997).
- Facilitates passage of feces through bowel through lubrication by the oil (Weiss and Fintelmann, 2000; De Smet *et al.*, 1997).
- Supports and develops brain function by increasing levels of docosahexaenoic acid (DHA), the major component of cell membranes of cerebral cortex and myelin sheaths (Horrobin, 1982; Simopouls, 1991).
- Reduces cholesterol levels by increasing prostaglandins E1 and E3 (PGE1 and PGE3), which inhibit cholesterol synthesis and stimulate cholesterol movement across cell membranes (Horrobin, 1982).
- Reduces platelet aggregation by increasing levels of PGE1 and PGE3 (Horrobin, 1982).
- Reduces inflammation by lowering arachidonic acid levels and driving synthesis of series 1 and 3 prostaglandins (Horrobin, 1982).
- Increases concentrations of sex hormone binding globulin (SHBG) by lignans (Adlercreutz *et al.*, 1987, 1992).
- Binds steroid hormones to its insoluble fiber, thereby reducing estrogen concentrations in circulation (Whitten and Shultz, 1988; Goldin *et al.*, 1982).
- Protects against degenerative disease by supplying omega-3 essential fatty acids (EFAs) (Budwig, 1953).

Contraindications

Ileus of any origin (flaxseeds) (Blumenthal *et al.*, 1998).

PREGNANCY AND LACTATION: No known restrictions. EFA supplementation during pregnancy and nursing is beneficial for fetal and infant brain development and visual function (Simopoulos, 1991; Horrobin, 1982).

Adverse Effects

None known at therapeutic dosages and following directions (i.e., consumption of adequate amounts of liquid, 1:10) (Blumenthal *et al.,* 1998).

Drug Interactions

As with any other mucilage, the whole or crushed seeds may negatively affect the absorption of other orally ingested drugs (Blumenthal *et al.,* 1998), although this is mainly speculative (Brinker, 2001). May also inhibit absorption of dietary nutrients (McGuffin *et al.,* 1997).

FLAX OIL: None known.

American Herbal Products Association (AHPA) Safety Rating

CLASS 2D: Can be safely consumed with the following restriction: Take with at least 150 ml (6 ounces) liquid. Contraindicated in bowel obstruction (i.e., flaxseeds).

Regulatory Status

AUSTRIA: Dried ripe seed official in the *Austrian Pharmacopoeia*, ÖAB (Meyer-Buchtela, 1999; Wichtl, 1997).

CANADA: Flaxseed is approved as a component of multiple-ingredient Schedule OTC (over-the-counter) Traditional Herbal Medicines (THMs), as a component of Schedule OTC nutritional agents, and as a single-ingredient homeopathic drug, all requiring premarket registration and assignment of a Drug Identification Number (DIN) (Health Canada, 2001).

CHINA: Dried ripe seed official in the *Pharmacopoeia of the People's Republic of China* (PPRC, 1997).

EUROPEAN UNION: Dried ripe seed official in the *European Pharmacopoeia* (Ph.Eur. 1997).

FRANCE: Dried ripe seed official in the *French Pharmacopoeia*, Ph.Fr.X (Bruneton, 1999).

GERMANY: Approved non-prescription drug of the German Commission E Monographs for both internal and external use (Blumenthal *et al.,* 1998). The gruel dosage form is an approved non-prescription drug of the *German Standard License* monographs (Braun *et al.,* 1996).

INDIA: Dried ripe seed official in the *Government of India Ayurvedic Pharmacopoeia of India* (API I, 1989) and is an approved single-drug dispensed in the Unani system of medicine (CCRUM, 1992).

SWEDEN: Component of multiple-herb products regulated as food without health claim (Tunón, 1999). As of January 2001, no flax products are listed in the Medical Products Agency (MPA) "Authorised Natural Remedies" (MPA, 2001).

SWITZERLAND: Dried, ripe seed official in the *Swiss Pharmacopoeia*, Ph.Helv. (Wichtl, 1997). Component of multiple-ingredient herbal medicines with positive classification (List D) by the *Interkantonale Konstrollstelle für Heilmittel* (IKS) and corresponding sales category D, with sale limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001; *Codex*, 2000/01).

U.K.: Linseed oil is on the *General Sale List*, Schedule 1 (medicinal product requiring a full product license), Table B (external use only) (GSL, 1994).

U.S.: Food or dietary supplement if structure-function label statement is made (USC, 1994).

Clinical Review

Eighteen studies are outlined in the following table, "Clinical Studies on Flax" including a total of 90,648 participants. All but two of these studies (Nordstrom *et al.*, 1995; McManus *et al.*, 1996), demonstrated positive effects for cardiovascular health, breast cancer, prostate cancer, lupus, and arthritis. One randomized, double-blind, placebo-controlled (R, DB, PC) study performed on 22 participants using flaxseed oil concluded that the duration of supplementation may have been too short to have an effect on rheumatoid arthritis, or that missing co-factors may have interfered with the clinical outcomes of this study (Nordstrom *et al.*, 1995). Two R, DB crossover trials found that flaxseed baked in food products produced a significant decrease in LDL cholesterol and in retarding the rate of bone resorption (Arjmandi *et al.*, 1998a; Arjmandi *et al.*, 1998b). In another study, consumption of flaxseed oil had no effect on glycemic control or insulin secretion (McManus *et al.*, 1996). A R, PC, single-blind, crossover trial found partially defatted flaxseed baked in food products reduced LDL serum cholesterol levels to concentrations associated with ingestion of full-fat flaxseed (Jenkins *et al.*, 1999). One study found secondary prevention of heart attack (De Lorgeril *et al.*, 1994). Two epidemiological reports found a reduction in the incidence of breast cancer or metastasis in women who used flaxseed oil (Bougnoux *et al.*, 1994; Willett *et al.*, 1992). One recent pilot study using flaxseed with and without a low-fat diet in older men with prostate cancer showed reduction in testosterone and prostate cancer cell proliferation rates and higher rates of apoptosis (Demark-Wahnefried *et al.,* 2001).

Branded Products

Alena™: ENRECO / P.O. Box 186 / Newton, WI 53063-0186 / U.S.A. / Tel.: 800-962-9536 / Fax: 920-926-4224 / Email: info@enreco.com / www.enreco.com. Ground stabilized flaxseed, 1,450 mg omega-3 fatty acids per tablespoon.

References

Aldercreutz H, Hockerstedt K, Bannwart C, *et al*. Effect of dietary components, including lignans and phytoestrogens, on enterohepatic circulation and liver metabolism of estrogens and on sex hormone binding globulin (SHBG). *J Steroid Biochem* 1987;27:1135–1144.

Aldercreutz H, Mousavi Y, Hockerstedt K. Diet and breast cancer. *Acta Oncol* 1992;31(2):175–81.

Allman, M, Pena M, Pang D. Supplementation with flax seed oil versus sunflower seed oil in healthy young men consuming a low fat diet: effects on platelet composition and function. *Eur J Clin Nutr* 1995;49(3):169–78.

API. See: *Ayurvedic Pharmacopoeia of India.*

Arjmandi B, Juma S, Lucas E, *et al*. Flaxseed supplementation positively influences bone metabolism in postmenopausal women. *J Am Nutraceutical Assn* 1998b;1(2):27–32.

Arjmandi B, Khan D, Juma S, *et al*. Whole flaxseed consumption lowers LDL-cholesterol and lipoprotein(a) concentrations in postmenopausal women. *Nutr Res* 1998a;18(7):1203–14.

Arya J, Caglj A. Exclusion of alpha-linolenic acid from diets for rats during several generations. I. Effect on reproduction and postnatal growth. *Arch-Latinoam-Nutr* 1993;43(2):123–31.

Ayurvedic Pharmacopoeia of India (API, Part I, Vol. I, 1st ed.). New Delhi, India: Government of India Ministry of Health and Family Welfare Department of Health; 1989;19.

Begin M, Ells G, Das U, *et al*. Differential killing of human carcinoma cells supplemented with n-3 and n-6 polyunsaturated fatty acids. *J Natl Cancer Inst* 1986;77(5):1053–62.

Bhatty RS. Nutrient Composition of Whole Flaxseed and Flaxseed Meal. In: Cunnane S and Thompson L. *Flaxseed in Human Nutrition.* Champaign, Ill: AOCS Press; 1995.

Bierenbaum, M, Reichstein R, Watkins T. Reducing atherogenic risk in hyperlipidemic humans with flaxseed supplementation: a preliminary report. *J Am Coll Nutr* 1993;12(5):501–4.

Blumenthal M, Busse WR, Goldberg A, Gruenwald J, Hall T, Riggins CW, Rister RS (eds.). Klein S, Rister RS (trans.). *The Complete German Commission E Monographs—Therapeutic Guide to Herbal Medicines*. Austin, TX: American Botanical Council; Boston: Integrative Medicine Communication; 1998.

Blumenthal M, Goldberg A, Brinckmann J (eds.). *Herbal Medicine – Expanded Commission E Monographs*. Newton, MA: Integrative Medicine Communications; 2000;201–4.

Bougnoux P, Koscielny S, Chajes V, *et al.* Alpha-linolenic acid content of adipose breast tissue: a host determinant of the risk of early metastasis in breast cancer. *Br J Cancer* 1994;70(2):330–4.

Braun R, Surmann P, Wendt R, Wichtl M, Ziegenmeyer J (eds.). *Standardzulassungen für Fertigarzneimittel – Text und Kommentar*, 11. Ergänzungslieferung. Stuttgart, Germany: Deutscher Apotheker Verlag; 1996 Feb;Zulassungsnummer 1099.99.99.

Brinker F. *Herb Contraindications and Drug Interactions* 3rd ed. Sandy, OR: Eclectic Medical Publications; 2001;96.

Bruneton J. *Pharmacognosy, Phytochemistry, Medicinal Plants*, 2nd ed. Paris, France: Lavoisier Publishing; 1999.

Budavari, S. (ed.). *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals,* 12th ed. Whitehouse Station, NJ: Merck & Co, Inc; 1996.

Budwig J. *The principal function of respiration in relation to the autoxidation of nutrient* [in German]. Freiburg: Hyperion Verlag; 1953.

Caughey G, Mantzioris E, Gibson R, *et al*. The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oils or fish oil. *Am J Clin Nutr* 1996;63(1):116–22.

CCRUM. See: Central Council for Research in Unani Medicine.

Central Council for Research in Unani Medicine (CCRUM). *Standardization of Single Drugs of Unani Medicine*, 1st Edition, Part II. New Delhi, India: Ministry of Health and Family Welfare, Government of India, CCRUM; 1992;276–81.

Clark W, Parbtani A, Huff M, *et al*. Flaxseed: A potential treatment of lupus nephritis. *Kidney Int* 1995;48(2):475–80.

Codex 2000/01: Die Schweizer Arzneimittel in einem Griff. Basel, Switzerland: Documed AG; 2000;111, 574, 578, 1039, 1402.

Cunnane S, Ganguli S, Menard C, *et al*. High alpha-linolenic acid flaxseed *(Linum usitatissimum):* some nutritional properties in humans. *Br J Nutr* 1993;69(2):443–453.

Cunnane SC, Hamadeh MJ, Liede AC*, et al.* Nutritional attributes of traditional flaxseed in healthy young adults. *Am J Clin Nutr* 1995;61(1):62–68.

de Lorgeril M, Renaud S, Mamelle N, *et al*. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343(8911):1454–9.

Delion S, Chalon S, Guilloteau D, *et al.* Alpha-linolenic acid dietary deficiency alters age-related changes of dopaminergic and serotoninergic neurotransmission in the rat frontal cortex. *J Neurochem* 1996;66:1582.

De Smet P, Keller K, Hansel R, *et al*. *Adverse effects of herbal drugs*, Vol. 2, Berlin, Germany: Springer-Verlag; 1997.

Delion S, Chalon S, Heralt J, *et al*. Chronic dietary alpha-linolenic acid deficiency alters dopaminergic and serotinergic neurotransmission in rats. *J Nutr* 1994;124(12):2466.

Demark-Wahnefried W, Price OT, Polzscik TJ *et al.* Pilot study of dietary fat restriction and flaxseed supplementation in men with prostate cancer before surgery: Exploring the effects of hormonal levels, prostate-specific antigen, and histopathological features. *Urology* 2001;58:47-52.

Erasmus U. Personal communication to T. Kunz. 2001.

ESCOP. 1997. "Lini semen." *Monographs on the Medicinal Uses of Plant Drugs.* Exeter, U.K.: European Scientific Cooperative on Phytotherapy; 1997.

Europäisches Arzneibuch, 3rd ed. (Ph.Eur.3). Stuttgart: Deutscher Apotheker Verlag; 1997.

Frances H, Monier C, Bourre J. Effects of dietary alpha-linolenic acid deficiency on neuromuscular and cognitive functions in mice. *Life Sci* 1995;57(21):1935.

Frances H, Monier C, Clement M, *et al*. Effect of dietary alpha-linolenic acid deficiency on habituation. *Life Sci* 1996;58(21):1805.

General Sale List (GSL). Statutory Instrument 1994 No. 2410 The Medicines (Products Other Than Veterinary Drugs) Amendment Order. London, U.K.: Her Majesty's Stationery Office (HMSO); 1994.

Goldin BR, Adlercreutz H, Gorbach SL, *et al*. Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. *N Eng J Med* 1982;307:1542–7.

GSL. See: *General Sale List*.

Haggans C, Hutchins A, Olson B, *et al.* Effect of flaxseed consumption on urinary estrogen metabolites in postmenopausal women. *Nutr Cancer* 1999;33(2):188–95.

Haggerty W. Flax: Ancient herb and modern medicine. *HerbalGram* 1999;45:51–7.

Health Canada. *Drug Product Database (DPD) Product Information*. Ottawa, Ontario: Health Canada; 2001.

Horrobin D. *Clinical Uses of Essential Fatty Acids*. London: Eden Press; 1982.

Ingram D, Sanders K, Kolybaba M, *et al*. Case-control study of phyto-estrogens and breast cancer. *Lancet* 1997;350(9083):990–4.

Jenab M, Thompson LU. The influence of flaxseed and lignans on colon carcinogenesis and β-glucuronidase activity. *Carcinogen* 1996;17(6):1343–8.

Jenkins D, Kendall C, Vidgen E, *et al*. 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;69:395–402.

Kelley D, Branch L, Love J, *et al*. Dietary alpha-linolenic acid and immunocompetence in humans. *Am J Clin Nutr* 1991;53(1):40–6.

Kelso KA, Cerrolini S, Speake BK. Effects of dietary supplementation with alpha-linolenic acid on the phospholipid fatty acid composition and quality of spermatozoa in cockerel from 24 to 72 weeks of age. *J Reprod Fertil* 1997;110(1):53–9

Kumar G, Das U. Free radical-dependent suppression of growth of mouse myeloma cells by alpha-linolenic acid and eicosapentaenoic acid *in vitro. Cancer Lett* 1995;92:27.

Lamptey M, Walker B. A possible essential role for dietary linolenic acid in the development of the young rat. *J Nutr* 1976;106:86–93.

Mazur W. Phytoestrogen content in foods. In: Adlercreutz H. (ed.). *Phytoestrogens.* London: Bailliere Tindall; 1998;12(4):729-742.

Mazur WM, Rasku S, Salakka A, *et al*. Lignan and isoflavonoid concentrations in tea and coffee. *Br J Nutr* 1998;79:37-45.

McGuffin M, Hobbs C, Upton R, Goldberg A (eds.). *American Herbal Products Association's Botanical Safety Handbook.* Boca Raton, FL: CRC Press; 1997.

McManus R, Jumson J, Finegood D, *et al*. A comparison of the effects of n-3 fatty acids from linseed oil and fish oil in well-controlled type 1 diabetes. *Diabetes Care* 1996;19(5):463–7.

Medical Products Agency (MPA). Naturläkemedel: Authorised Natural Remedies (as of January 24, 2001). Uppsala, Sweden: Medical Products Agency; 2001.

Meyer-Buchtela E. *Tee-Rezepturen: Ein Handbuch für Apotheker und Ärzte.* Stuttgart, Germany: Deutscher Apotheker Verlag. 1999; Leinsamen.

Morant J, Ruppanner H (eds.). Bioforce Linoforce. In: *Arzneimittel-Kompendium der Schweiz*® 2001. Basel, Switzerland: Documed AG; 2001;728.

MPA. See: Medical Products Agency.

Muir AD, Westcott ND. Quantitation of the Lignan Secoisolariciresinol Diglucoside in Baked Goods Containing Flax Seed or Flax Meal. *J Agric Food Chem* 2000;48:4048-4052.

Nesbitt P, Thompson L. Lignans in homemade and commercial products containing flaxseed. *Nutr Cancer* 1997;29(3):222–7.

Nestel P, Pomeroy S, Sasahara T, *et al*. 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):1163–70.

Nordstrom D, Honkanen V, Nasu Y, *et al*. Alpha-linolenic acid in the treatment of rheumatoid arthritis. A double-blind, placebo-controlled and randomized study: flaxseed vs. safflower seed. *Rheumatol Int* 1995;14:231–4.

Ph.Eur. See: *Europäisches Arzneibuch*.

Pharmacopoeia of the People's Republic of China (PPRC English Edition Volume I 1997). Beijing, China: Chemical Industry Press; 1997;217.

Phipps W, Martini M, Lampe J, *et al*. Effect of flaxseed ingestion on the menstrual cycle. *J Clin Endrocrin Metab* 1993;77(5):1215–9.

PPRC. See: *Pharmacopoeia of the People's Republic of* China.

Prasad K. Dietary flax seed in prevention of hypercholesterolemic atherosclerosis. *Atherosclerosis* 1997;132(1):69–76.

Serraino M, Thompson L. The effect of flaxseed supplementation on the initiation and promotional stages of mammary tumor genesis. *Nutr Cancer* 1992a;17(2):153–9.

Serraino M, Thompson L. Flaxseed supplementation and early markers of colon carcinogenesis. *Cancer Lett* 1992b;63(2):159–65.

Serraino M, Thompson L. The effect of flaxseed supplementation on early risk markers for mammary carcinogenesis. *Cancer Lett* 1991;60(2):135–42.

Simopoulos A. Omega-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr* 1991;54:438–63.

Thompson LU, Robb P, Serraino M, Cheung F. Mammalian lignan production from various foods. *Nutr Cancer* 1991;16:43-52.

Thompson LU, Rickard S, Orcheson L, Seidl MM. Flaxseed and its lignan and oil components reduce mammary tumor growth at a late stage of carcinogenesis. *Carcinogenesis* 1996;17(6):1373-1376.

Tunón H. Phytotherapie in Schweden. *Z Phytother* 1999;20:268–77.

United States Congress (USC). Public Law 103–417: Dietary Supplement Health and Education Act of 1994. Washington, DC: 103rd Congress of the United States; 1994.

USC. See: United States Congress.

Walker B. Maternal diet and brain fatty acids in young rats. *Lipids* 1967;2:497–500.

Weiss R, Fintelmann V. *Herbal Medicine.* Stuttgart: Thieme; 2000.

Whitten C, Shultz T. Binding of steroid hormones *in vitro* by water insoluble dietary fiber. *Nutr Res* 1988;8:1223–35.

Wichtl M (ed.). *Teedrogen und Phytopharmaka, 3. Auflage: Ein Handbuch für die Praxis auf wissenschaftlicher Grundlage*. Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft mbH. 1997;346-350.

Willet W, Hunter D, Stampfer M, *et al*. Dietary fat and fiber in relation to risk of breast cancer. An 8-year follow-up. *JAMA* 1992;268(15):2037–44.

Clinical Studies on Flax (*Linum usitatissimum* L.)

Cardiovascular

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Jenkins *et al*., 1999	Effects on serum lipids, indicators of oxidation stress, and *ex vivo* sex hormone activities	R, SB, PC CO n=29 hyperlipidemic subjects (mean age 57 years)	3 periods: 1. 3 weeks treatment 2. 2 weeks wash-out 3. 3 weeks CO treatment	50 g/day	Partially defatted flaxseed meal baked in muffins	Significant reduction in total cholesterol (p=0.001), LDL serum cholesterol (p=0.001), and apolipoprotein (p=0.005) level with partially defatted flaxseed. No significant change in HDL cholesterol, serum protein carbonyl content, or *ex vivo* androgen or progestin activity with either treatment.
Arjmandi *et al*., 1998a	Effect on lipid profile	R, DB, CO n=38 severely hypercholesterolemic, post-menopausal women (mean age 56.3 years)	6 weeks treatment with flaxseed or sunflower seed; 2 weeks wash-out; 6 weeks CO to other seed	38 g/day	Flaxseed baked in bread and muffins or sunflower seed	Flaxseed significantly lowered LDL cholesterol (p<0.02) vs. sunflower seed. Serum Lp(a) decreased significantly with flaxseed (p<0.05). No effect on HDL cholesterol or triglycerides levels.
Nestel *et al*., 1997	Effect on arterial compliance	CC n=15 obese persons with markers of insulin resistance, mean BMI, 30.4 kg/m^2 (mean age 54 years)	16 weeks (4 periods of 4 weeks each) 1. Saturated/ high fat 2. Alpha-linolenic acid (ALA) /low fat 3. Oleic acid/low fat 4. High fat	2732 ± 533 kcal/3 days 20g ALA daily	Baked biscuits and muffins with purified deodorized flaxseed oil or Sunola oil (oleic acid-rich oil)	Significant increase in arterial compliance with flaxseed (p<0.0001) and with oleic acid (p<0.05). Significant decrease in mean arterial pressure with flaxseed (p<0.05) and with oleic acid (p<0.05). Significant decrease in HDL cholesterol with flaxseed (p<0.01) vs. oleic acid and control. Significant increase in insulin response with flaxseed vs. control (p=0.016).
Allman *et al*., 1995	Effect on platelet composition and function	R, P n=11 healthy non-smokers, mean BMI, < 30 kg/m^2 (mean age 22 years)	23 days	40 g/day flaxseed oil or sunflower oil	Flaxseed oil or sunflower oil	Improved platelet composition by 2x increase in platelet EPA (p<0.05) levels with ALA. Reduced platelet aggregation response (p<0.05) with alpha-linolenic acid.
De Lorgeril *et al*., 1994	Secondary prevention of myocardial infarction	R, MC, SB, P n=605 patients who had a myocardial infarction (MI) (n=302 treatment group; n=303 control group)	5 years	19 g/day	Flax-based spread substitution plus Mediterranean diet (rich in ALA)	Treatment group had 76% lower incidence of deaths due to MI and 70% lower mortality rate than control. 3x increase in omega-3 intake combined with decrease in saturated fat, cholesterol, and omega-6 intake reduces risk of second MI (adjusted risk rate=0.27; p=0.001).
Bierenbaum et al., 1993	Atherogenic risk	O n=15 subjects with hyperlipidemia on long-term vitamin E (800 IU/day) (mean age 52.2 years)	3 months	15 g/day plus 3 slices of 10% flaxseed bread	Ground flaxseed (flour) in diet	Significantly decreased both total cholesterol (p<0.01) and LDL cholesterol (p<0.01). Lack of effect on HDL cholesterol. ATP measurements suggest flax inhibits platelet aggregation.

KEY: C – controlled, **CC** – case-control, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.

Clinical Studies on Flax (*Linum usitatissimum* L.) (cont.)

Breast Cancer

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Haggans *et al*., 1999	Estrogen excretion	R, CO n=28 healthy post-menopausal women, non-smokers, mean BMI, 23.9 kg/m^2 (mean age 68.3 years)	Three 7-week periods: 2 periods with flaxseed; 1 period as control	5–10 g/day (as single daily dose)	Raw, ground flaxseed vs. usual diet	Significant increase in urinary estrogen metabolites, 2-hydroxyestrogen ($p<0.05$) and 16-alpha-hydroxyestrone ($p<0.0005$). Suggests flaxseed may protect against breast cancer.
Ingram *et al*., 1997	Risk breast cancer	CC n=144 subjects with newly diagnosed breast cancer vs. matched women without breast cancer living in the same ZIP code area (ages 30–84 years)	23 months	Not applicable	Dietary intake of phyto-estrogens	Substantial reduction in breast cancer risk among women with high intake of phytoestrogens, as assessed by significant increase in excretion of equol ($p=0.009$) and enterolactone ($p=0.013$).
Phipps *et al*., 1993	Effect on menstrual cycle and serum hormone concentration	R, CO n=18 healthy women with regular menstrual cycle length (25-30 days) (ages 20–34 years)	7 consecutive menstrual cycles	10 g/day 2x 5 g or 3x 3.33 g	Raw flaxseed powder	Flaxseed associated with longer luteal phase ($p=0.002$), increased longer luteal phase estradiol ratios, and few anovulatory cycles. Overall, decreased tendency for ovarian dysfunction, which possibly decreases risk for breast cancer.
Bougnoux *et al*., 1994	Assessment of ALA content in adipose breast tissue and metastasis	E, P n=121 patients with initially localized breast cancer	Followed for 31 months	Not applicable	Dietary intake of fatty acids	Predictive factors for occurrence of metastasis are related to large tumor size and low levels of ALA in adipose breast tissue of breast cancer patients. Suggests low levels of ALA have a role in the metastatic process *in vivo*.
Willett *et al*., 1992	Breast cancer risk	E, P n=89,494 registered nurses (ages 34–59 years)	8 years	Not applicable	Dietary intake of alpha-linolenic acid	No evidence of association between total fat intake and dietary fiber intake in middle-aged women.

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Clinical Studies on Flax (*Linum usitatissimum* L.) (cont.)

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Demark-Wahnefried, 2001	Prostate cancer	PS n=25 men with prostate cancer (mean age 64 years)	Average 34 days (21–77 days)	30 g flaxseed meal (3 rounded Tblsp.)	Alena™	This study with and without a low-fat diet supplemented with flax showed significant decrease in total testosterone ($p<0.001$), lower cell proliferation rates, and higher apoptosis rates associated with short-term dietary intervention and flaxseed. PSA levels decreased among men who had biopsy Gleason sums of 6 or less and continued to rise among men with higher Gleason sums (despite evidence of lower rates of proliferation and higher rates of apoptosis).
Arjmandi *et al.*, 1998b	Osteoporosis	R, DB, CO n=38 healthy, non-smoking, post-menopausal women not receiving hormone replacement therapy (mean age 56.3 years)	6 weeks treatment followed by 2-week wash-out followed by 6 weeks of treatment	38 g/day	Flaxseed or sunflower seed (control) baked in muffins and bread	Flaxseed treatment significantly lowered tartrate resistant acid phosphatase activity in serum (a marker of bone resorption) ($p<0.05$). No effect on insulin-like growth factor and insulin-like growth factor protein-3 concentration (serum bone-specific). No effect on total alkaline phosphatase activity (marker of bone formation), and 17b estradiol levels. Tendency to decrease urinary excretions of both hydrooxyproline and calcium. Flaxseed may not enhance bone formation, but may slow down the rate of bone resorption.
Caughey *et al.*, 1996	Effect on cytokine production	Cm, PG n=15 healthy subjects (ages 24–44 years)	2 months	13.7 g/day ALA or 9 g/day fish oil (1.62 g EPA/day and 1.08 g DHA/day)	Flaxseed oil and flaxseed oil plus butter spread as dietary substitutions vs. sunflower oil	Vegetable oils rich in n-3 fatty acids inhibit TNF-alpha and IL-1-betasynthesis. This finding is significant, as these factors are implicated in inflammatory rheumatoid arthritis ($p<0.05$) and atherosclerosis ($p<0.05$).
McManus *et al.*, 1996	Non-insulin dependent diabetes	R, DB, CO n=11 (mean age 61.8 years)	3 months	35 mg/kg/day	Flaxseed oil capsules or olive oil (control)	Neither oil significantly affected glycemic control or insulin secretion.
Clark *et al.*, 1995	Lupus nephritis	O n=9 subjects with documented systemic lupus erythematosus, history of positive ANA, and with proteinuria >1 g/24 hours	17 weeks	Weeks 1–4: 15 g/day; Weeks 5–8: 15 g 2xday; Weeks 9–12: 15 g 3xday; Followed by 5-week wash-out period.	Crude flaxseed	Flaxseed was well-tolerated at 15 and 30 g/day, but not well-tolerated at 45 g/day. Total and LDL cholesterol levels and whole blood viscosity decreased significantly with 30 g/day. Reduction of serum creatine with 30 g and 45 g/day. Increase in creatinine clearance with 15 g and 30 g/day.
Nordstrom *et al.*, 1995	Rheumatoid arthritis	R, DB, PC n=22 (mean age treatment group, 51 years; mean age control group, 53 years)	3 months	30 g/day	Flaxseed oil or safflower oil (control)	No statistical alterations or effects were found. Concluded supplementation may have been for too short of a term, or low intake of zinc impaired EFA conversion.
Cunnane *et al.*, 1995	Nutritional status	R, CO n=10 healthy non-smokers (mean age 25 years)	1 month	50 g/day	Muffins with milled flaxseed or muffins without flaxseed	Significant reduction in total cholesterol ($p<0.05$) and LDL cholesterol ($p<0.05$) with flaxseed. No change in HDL cholesterol or triglycerides. Increased number of bowel movements ($p<0.05$) with flaxseed.

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