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## Flaxseed as Functional Food.

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### ABSTRACT

Flaxseed is one of the most important oilseed crops for industrial as well as food, feed, and fiber purposes. The seed provides oil rich in essential fatty acids, digestible proteins, and lignans. Being one of the richest sources of  $\alpha$ -linolenic acid oil and lignans, flaxseed has considerable potential as a functional food. It delivers health benefits beyond their traditional nutrient content. Phytoestrogen of flaxseed is in focus for their benefits for a wide range of health conditions and may possess chemo-protective properties in animals and humans. This paper presents a review for the nutritional composition of flaxseed, its health benefits for disease prevention specially those relevant to cardiovascular system, diabetes, menopause, cancer, arthritis and dry eye.

**Keywords:** flaxseed, food, oil.

## INTRODUCTION

Flax (*Linum usitatissimum*) is a plant of the family Linaceae [1] with pale blue flower and brown to yellow oval flat seeds with pointed tips, slightly bigger than sesame seeds 4-6 mm. Audible type is commonly called flaxseed (FS) while that used in industry is known as linseed. The seeds have crisp and chewy texture and a pleasant, nutty taste. Flax continues to surge forward in its recognition as a functional food as it is rich in essential fatty acids, dietary fiber and proteins. This review will go through the flax benefits trying to give brief description of chemical composition and review the beneficial effect for various ailments such as cardiovascular disease, diabetes, menopausal disorders, cancer, arthritis, dry eye and others.

### Composition of flaxseed (FS) and flaxseed oil (FO)

The composition of flax varies with genetics, growing environment, seed processing and method of analysis [2]. FS and FO is superior in its composition compared to other edible fats and oils as it contains ALA (omega3) as well as linoleic acid LA (omega6) in specific ratio that make them more beneficial. These two polyunsaturated fatty acids are essential for human but our bodies cannot synthesis them and should be obtained from food. Analysis of different dietary oils and fats showed that flaxseed (FS) has the highest percentage of ALA (omega3) compared to other plant derived fats [3]. ALA constitutes 57%, Linoleic acid constitutes 16% while the nutritionally undesirable saturated fatty acids presents only 9% of total fatty acids of flax. [4]

**Protein:** flax contains 18.3% protein [4]. Pattern of flax protein is similar to that of soybean protein, which is viewed as one of the most nutritious plant proteins. Flax has rich content of essential amino acids, the body cannot form, and is gluten-free [5] so flax is suitable for patients with celiac disease [6].

**Carbohydrates:** Flax is low in carbohydrates (sugars and starches), providing only 1.5 gram (g) per 100 g [4].

**Dietary fiber:** Total fiber accounts about 28% of the weight of flax seeds, composed of Cellulose, Mucilage gums, Lignin and Lignans that not digested by the human and, therefore, pass relatively intact into the large intestine [7]. Dietary fiber acts as a bulking agent in gut. It increases stool weight and the viscosity of digested material, while also decreasing the transit time of material through the gut helping to control appetite and blood glucose and reduces blood lipids. [8].

**Phenolics:** phenolics have anticancer and antioxidant effects in humans [9,10]. Flax contains Phenolic Acids, Flavonoids and lignans. It contains about 8 to 10 mg of total phenolic acids per 100gm or about 64-80 milligrams (mg) of total phenolic acids/tbsp of milled flax. Concerning flavenoid, flax contains about 35-70 mg of total flavonoids/100g which is equivalent to about 2.8-5.6 mg of flavonoids/tbsp of milled flax [11]. Lignans plays an important role in cancer prevention and is considered as main source of plant estrogen, with good effect as antioxidants. Flax contains up to 800 times more lignans than other plant food. [12].

### Vitamin and mineral content of flax:

Flax contains minor amounts of water- soluble vitamins like vit. B<sub>1,2,3,5,6</sub> and fat-soluble vitamins like vitamin E which is present as gamma-tocopherol that protects cell proteins and fats from oxidation; promotes sodium excretion in the urine, which may lower blood pressure; and decrease risk of heart disease, some types of cancer [13]. The gamma-tocopherol content can range from 8.5 to 39.5 mg/100 g of seed or about 0.7-3.2 mg/tbsp of milled flax. Flax contains a small amount of Vitamin K (0.3 microgram/g) in the form of phyloquinone, the plant form of the vitamin, which plays an essential role in blood clotting and bone health. The mineral content of one tablespoon of milled flax contains 34 mg of magnesium (392mg/100gm). 66 mg of potassium (813mg/100gm) while sodium is minimal [6].

### Biologic Effects of FS and FO in health and disease:

Both ALA and LA are essential fatty acids (EFA) which must be supplied in diet as the body cannot manufacture them. EFAs are required for the structure and flexibility of cell membrane. They are precursors of long-chain fatty acids converted to powerful compounds that affect many biological processes as inflammation and cell signaling. EFAs affect gene expression and cell protein formation [14] and have antibacterial actions. ALA is the precursor of all omega 3 long chain FA manufactured in the body while LA is the precursor of all

omega 6 long chain FA and arachidonic acid FA. The enzymes used in such metabolic steps are the same. Competition can occur between the two families, the more LA is present the less the conversion of ALA to beneficial eicosanoids [3]. About 96% of dietary ALA appears to be absorbed in the gut [15]. After absorption, ALA has several metabolic fates either undergo  $\beta$ -oxidation to produce energy, recycled to make other fatty acids, serve as a substrate for ketogenesis, stored in adipose tissue for later use, incorporated into the phospholipids of cell membranes or it can be converted to long-chain omega-3 fatty acids like eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA), which have important functions in many types of cells and organs.

Gender can affect the conversion of ALA where women can convert more ALA to EPA and HDA than men. Estrogen appears to enhance this process as women need DHA during pregnancy and lactation [16].

Other dietary factors that interfere with ALA conversion include the intake of dietary cholesterol [17] and saturated fat [18]. Also, smoking had a negative effect on the metabolism of omega-3 fatty acids in human breast cells [19] and decrease the conversion to EPA and DHA. LA is converted through the same pathway as ALA but to arachidonic acid (AA) which is converted to another type of eicosinoid (thromboxan A<sub>2</sub>, leukotarin B<sub>4</sub>) which promote both the clotting of blood within blood vessels (thrombosis) and inflammatory reactions. Diets high in LA or AA may result in increase of AA-derived eicosanoids that, in turn, may result in an over-active immune system that result in chronic diseases like coronary heart disease, diabetes and cancer [20]. This eicosanoid is Docosapentaenoic acid (DPA) with the formula 22:5n-6 is a member of the omega-6 family. It should not be confused with the omega-3 DPA (22:5n-3) which plays anti-inflammatory action.

Biological activity of flax is attributed to ALA and its derivatives EPA and DHA that make them useful in preventing and managing chronic conditions such as type 2 diabetes, kidney disease, rheumatoid arthritis, high blood pressure, coronary heart disease, stroke, Alzheimer disease, and certain types of cancer.

#### **Effect of FS, FO during pregnancy and lactation**

The growing fetus is supplied by essential fatty acids from the mother through the placenta. For this reason, pregnant women must eat a diet containing adequate amounts of omega-3 and omega-6 fats for her own needs and also for those of the developing fetus. The DHA and arachidonic acid derived from essential fatty acids are especially vital, as they are building materials for the structure of nervous tissue of growing fetus, including the brain and retina in late pregnancy [21]. Breast milk contains 3-10 times more ALA than DHA, depending on the mother's diet [20]. Children born to mothers who took DHA (present in flax or cod liver oil) during pregnancy and lactation scored higher IQ at 4 years old compared with children whose mother's diets were supplemented with corn oil. [22].

#### **Hormone regulatory function of FS**

The effect of the ingestion of flax seed powder, known to produce high concentrations of urinary lignans in cycling women. Studies showed that women who supplemented with FS for three cycles showed ovulation associated with longer luteal phase in comparison to others not supplemented with FS who showed 2 out of three anovulatory cycles despite of the non significant differences in either estradiol or estrone during all phases of the cycle in both groups [ 23 ] . Authors stated that FS ingestion had no effect on early follicular phase hormone concentrations (estradiol, estrone, progesterone) or sex hormone-binding globulin and referred the effect to flax to a specific role for lignans and the relationship between the dietary and natural sex steroid action. They suggested a possible role of FS to control the risk of breast and other hormonally dependent cancers [23].

Ten years before the cessation of menstrual cycle and at midlife, women suffer the peri-menopausal symptoms such as irregular menstrual cycles, breast cysts, headaches, insomnia, fluid retention, anxiety, irritability, mood swings, weight gain, lowered sex drive, brain fog, fibroid tumors, and heavy bleeding. The most probable cause of all these problems is estrogen dominance while progesterone levels steadily decline. As flaxseed regulates normal ovulation and prolong the luteal phase of the menstrual cycle, in which progesterone is the dominant hormone and respectively restore hormonal balance [24].

**FS and bone formation:**

FS and FO are beneficial to women having osteoporosis. Regulation of bone formation is due to equilibrium between Sexual steroids, thyroid hormones, glycocorticoids and growth hormone are the maestro of this regulation. As estrogen ceases during menopause, bone resorption increases [25]. FS contains phytoestrogens such as daidzein and genistein that were proven to have an anabolic effect on bone metabolism and prevent bone loss [26]. Phytoestrogen is a biologically active plant group with chemical structure similar to estradiol and can bind to estrogen receptors in various cells [27]. Phytoestrogens may also exert their biological effects via nonestrogen receptor. It inhibits the activity of several enzymes such as protein tyrosine kinases, DNA topoisomerase I (EC 5.99.1.2) , DNA topoisomerase II (EC5.99.1.3) [28], and ribosomal S6 kinase , which are involved in cell-signaling mechanisms and nuclear events such as cell proliferation and differentiation.

Additionally, phytoestrogens are known to have potent antioxidant activity [29]. Lignans are structurally similar to tamoxifen. It inhibits the TNF- $\alpha$  biosynthesis and consequently IL-1 & IL-6 in stromal and osteoblastic cells [30] that cause bone resorption [31]. Flaxseed is a very rich source of  $\alpha$ -linolenic acid , which is known to decrease bone turnover and increase bone mineral density in the femur and lumber bones[32]. ALA acid is a precursor to Eicosapentaenoic acid (EPA) that has generated interest as a potential anti-inflammatory agent. [33, 34].

The omega-3 fat found in flaxseed prevent excessive bone turnover, subjects' blood levels of N-telopeptides, a marker of bone breakdown were found to be much lower following the omega-3-rich diet. [35]

**FS and breast Cancer:**

Flaxseed lignans are converted by beneficial gut flora into two hormone-like substances called enterolactone and enterodiol that have a protective effects against breast cancer. Studies show that women with breast cancer typically excrete much lower levels of lignans in their urine than women without breast cancer. Animal studies conducted to evaluate lignans' beneficial effect, supplementing a high-fat diet with flaxseed flour reduced early markers for mammary (breast) cancer in laboratory animals by more than 55%. [36]. When postmenopausal women ate a daily muffin containing flaxseed showed higher level of 2-hydroxyestrone, a less biologically active estrogen metabolite thought to be protective against breast cancer. While the level of 16 $\alpha$ -hydroxyestrone (an estrogen metabolite thought to promote cancer) decreased.

So Eating about an ounce of ground flaxseed each day will affect the way estrogen is handled in postmenopausal women in such a way that offers protection against breast cancer and not interfere with estrogen's role in normal bone maintenance [36].

**Effect of FS and vascular disease:**

The term cardiovascular disease (CVD) refers to all diseases of the blood vessels and circulation system, including heart attacks and stroke. The main nutrients in flax particularly, alpha-linolenic acid (ALA), dietary fiber; and the lignan (SDG) contribute to its healthy effects on CV system [1]. Nutritionists advise paying attention to the kinds of fats eaten. They suggest you have to eat less saturated fat (SF) and trans-fats (TF) but more polyunsaturated fat (PUF) which is provided by flax.

Studies showed that diet high in ALA reduces the risk of heart disease by lowering cholesterol level and preventing the buildup of harmful deposits in arteries [37]. Over time, with exposure to risk factors as cigarette smoke, high blood glucose (diabetes), high blood cholesterol, high blood Pressure, diet composition and low physical activity, all damages the endothelium and increases inflammatory reactions leading to CVD.

Eating food rich in fiber, such as flaxseed may prevent heart disease. Almost 10,000 adult Americans participated in this study and were followed up for 19 years. the study showed that people fed on high fiber diets (21 grams per day) had 12% less CVD compared to others consumed 5 grams of fibers daily. This may be referred to the beneficial effect of ALA [38, 39].

Atherosclerosis begins in childhood and involves unhealthy changes in the lining of blood vessels or endothelium. The endothelium maintains vascular homeostasis by controlling the balance between agents

causing vasodilatation and vasoconstriction, Also preserving vascular homeostasis by balancing the actions of clotting and anti-clotting agents. When the endothelium becomes inflamed, cholesterol and other lipids especially low density lipoproteins LDL begin to accumulate in blood vessel walls. This process is a complex series of events involving increased oxidative stress and the release of inflammatory compounds like harmful eicosanoids, cytokines and acute-phase proteins. like interleukin-1 $\beta$  (IL-  $\beta$ ) interleukin-6 (IL-6), tumor necrosis factor  $\alpha$ (TNF $\alpha$ ). In response to these cytokines, cell adhesion molecules (CAM) are released and promote the sticking of white blood cells to the endothelium [40].Vascular cell adhesion molecule type 1 (VCAM-1), intercellular adhesion molecule type 1 (ICAM-1) plaque is formed consequently cause thrombus which block the blood supply to the vital organs supplied by this vessel causing infarction.[37].

Flaxseeds and Walnut, ALA-rich vegetable oils and omega-3 fats in general improve endothelial function and increase vasodilatation [41]. previous study showed that elderly men, who fed on ALA rich vegetable oils have the lowest risk of heart attack and fatal heart disease. decrease blood levels of cell adhesion molecules CAM. Which are considered as biomarkers of early events in the development of atherosclerosis. [42]

In another study authors mentioned that n-3 PUFA consumption lowers plasma triglycerides, resting heart rate, and blood pressure and might also improve myocardial filling and efficiency, lower inflammation, and improve vascular function. Experimental studies demonstrate direct anti-arrhythmic effects, which have been challenging to document in humans, but this effect was to lesser extent as regard fatal outcome of stroke or myocardial infarction.[43]

Also, studies suggested that flax lignans have a lowering effect on plasma total and low-density lipoprotein cholesterol. The associations between lignans and decreased risk of cardiovascular disease are promising, but they are yet not well established [44]. Decrease of cholesterol by flaxseed ingestion was documented in animal study [45]. The researchers also found that omega-3s from nuts, seeds, and vegetable oils , such as walnuts and flaxseed, had just as much impact on blood pressure as omega-3s from fish. [46]. Healthy menopausal women who consumed 40 g (5 tbsp) of milled flax daily for one year experienced significant reductions of 5% in systolic blood pressure and 4.1% in diastolic blood pressure at 12 months [47]. The findings from these few studies suggest that interventions of at least 3 months are needed to show an effect of flax consumption on blood pressure [48].

#### **Effect of FS, FO on inflammatory disease and arthritis**

FO eases symptoms of rheumatoid arthritis, Lubricates joints and lessens stiffness and joint pain as it is high in alpha-linolenic acid (ALA), a type of omega-3 fatty acids which are known as anti inflammatory.

Both tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) and interleukin I  $\beta$  ( IL- I  $\beta$ 3) have been implicated as mediators of the joint pathology that occurs in the inflammatory disorder rheumatoid arthritis (RA) and as mediators of the cellular pathology including synovial hyperplasia . [49]

Use of flaxseed oil in domestic food preparation for 4 wk inhibited TNF  $\alpha$  and IL-1  $\beta$  production by approximately 30%.There was a significant inverse exponential relation between TNF  $\alpha$  or IL-1 $\beta$  synthesis and mononuclear cell content of eicosapentaenoic acid (EPA), an n-3 fatty acid of ingested alpha-linolenic acid (flaxseed oil). Cytokine production decreased as cellular EPA increased to approximately 1% of total fatty acids [49].

#### **Effect of FS on diabetes and obesity**

Cell membranes are the cells' gatekeepers, allowing the flow of needed nutrients while promoting the elimination of wastes. Flexible cell membranes respond to insulin and absorb glucose better than the rigid non flexible membranes that result from high saturated and/or hydrogenated (trans) fats, rich diets. Dietary fiber such as flaxseed may help to reduce the risk of diabetes and obesity because it have the omega-3 fats that are needed to produce flexible cell membranes [15].

Oxidative stress has been shown to be one of the causes of both type 1 and type 2 diabetes. Secoisolariciresinol diglucoside (SDG) is isolated from flaxseed and has antioxidant activity. It can prevent hypercholesterolemic atherosclerosis and development of diabetes in rats. Also studying a model of human

type I diabetes [insulin dependent diabetes mellitus (IDDM)] showed that SDG prevents the development of diabetes via its antioxidant effect [50].

Studies on the role of flaxseed and its components in obesity and diabetes in humans are few. In healthy females, 50 g carbohydrate from flaxseed or 25 g flaxseed mucilage (soluble fiber) lowered postprandial glucose by 27%. and lowered serum cholesterol [51]. Flaxseed oil significantly improved insulin sensitivity, increased HDL cholesterol, and decreased LDL oxidation [52].

#### **Effect of FS on cancer**

Flaxseed ingestion proved anticarcinogenic effect in colon. Following a single injection of azoxymethane (15 mg/kg body wt.) , rats were fed 5% or 10% flaxseed meal (FM) or flaxseed flour (FF) for four weeks showed less number of aberrant crypts and foci, in histological examination of intestinal section, by 41-53% and 48-57%, respectively. The labeling index (LI) was also 10-22% lower in these groups, except for the 5% FM group [53]. Since lignans have been suggested to have some cancer-protective effects, flaxseed , the most abundant source of lignan precursors, reduced the epithelial cell proliferation by 38.8-55.4% and nuclear aberrations by 58.8-65.9% in female rat mammary gland[54].

Also, flaxseed reduced the formation, growth and spread of prostate cancer and melanoma. As well it enhanced the effectiveness of tamoxifen, a standard drug for hormonal therapy of breast cancer [55,56]

#### **Effect of FS on eye**

Dry eye syndrome (DES) affects more than 10 million Americans. Artificial tears offer only temporary relief. Study involving nearly 40,000 female aged 45-84 , enrolled in the Women's Health study Researcher, to know whether omega-3 fats (found in high amounts in cold water fish and flaxseeds), and the omega-6 fats (found in red meat, safflower, sunflower, soy and corn oils) play a role in treatment. Women whose diets provided the highest amounts of omega-3 fatty acids had a 17% lower risk of dry eye syndrome compared with those consuming the least of these beneficial fats. In contrast, women whose diets supplied a high ratio of omega-6 to omega-3 fatty acids had a 2.5-fold higher risk of DES syndrome compared to those with a more balanced intake of fatty acids [57].

#### **REFERENCES**

- [1] Hasler CM. 2002. Functional foods: Benefits, concerns and challenges - A position paper from the American Council on Science and Health. *J. Nutr.* 132: 3772-3781.
- [2] Daun JK, Barthet VJ, Chornick TL, Duguid S. 2003. Structure, composition, and variety development of flaxseed. In: *Flaxseed in Human Nutrition*, eds Thompson LU and Cunnane SC, 2nd ed, AOCS Press, Champaign, IL, p 1-40.
- [3] Diane H. Morris. 2007 *Flax - A Health and Nutrition Primer* , 4th Edit. Winnipeg: Flax Council of Canada
- [4] Nutrient Data Laboratory, Beltsville Human Nutrition Research Center, Agricultural Research Service, 2011. USDA National Nutrient Database for Standard Reference, Release 24 [Internet]. [cited 2012 jan]. Available from: <http://www.ars.usda.gov/nutrientdata>
- [5] Aubrecht E, Horacek M, Gelencser E, Dworschak E. 1998. Investigation of prolamin content of cereals and different plant seeds. *Acta Alimentaria* 27: 119-125.
- [6] Branski D, Fasano A, Troncone R. 2006. Latest developments in the pathogenesis and treatment of celiac disease. *J. Pediatr.* 149: 295-300
- [7] Safe S, Papineni S. 2006. The role of xenoestrogenic compounds in the development of breast cancer. *Trends Pharma. Sci.* 27: 447-454.
- [8] Brennan CS. 2005. Dietary fibre, glycaemic response, and diabetes. *Mol. Nutr. Food Res.* 49: 560-570
- [9] Naczki M, Shahidi F. 2006. Phenolics in cereals, fruits and vegetables: occurrence, extraction and analysis. *J. Pharma. Biomed. Anal.* 41: 1523-1542.
- [10] Dashwood RH. 2007. Frontiers in polyphenols and cancer prevention. *J. Nutr.* 137: 2675-2695.
- [11] Oomah BD, Mazza G. 1998. Flaxseed products for disease prevention. In: *Functional Foods: Biochemical & Processing Aspects*, ed Mazza G, Technomic Publishing, Lancaster, PA, p 91-138
- [12] Muir AD. 2006. Flax lignans – analytical methods and how they influence our understanding of biological activity. *J. AOAC Int.* 89: 1147-1157.
- [13] Sen CK, Khanna S, Roy S. 2006. Tocotrienols: vitamin E beyond tocopherols. *Life Sci.* 78: 2088-2098.

- [14] Horia E, Watkins BA. 2005. Comparison of stearidonic acid and  $\alpha$ -linolenic acid on PGE2 production and COX-2 protein levels in MDA-MB-231 breast cancer cell cultures. *J. Nutr. Biochem.* 16: 184-192.
- [15] Das UN. 2006. Essential fatty acids *Curr. Pharma. Biotechnol.* 7: 467-482.
- [16] Silva MHL, Silva TLC, Brandão SCC, 2005. Fatty acid composition of mature breast milk in Brazilian women. *Food Chem.* 93: 297-303.
- [17] Burdge GC, Calder PC. 2005. Conversion of  $\alpha$ -linolenic acid to longer-chain polyunsaturated fatty acids in human adults. *Reprod. Nutr. Dev.* 45: 581-597.
- [18] Freemantle E, Vandal M, Tremblay-Mercier J, 2006. Omega-3 fatty acids, energy substrates, and brain function during aging. *Prostaglandins Leukot. Essent. Fatty Acids* 75: 213-220.
- [19] Liou YA, King DJ, Zibrik D, Innis SM. 2007. Decreasing linoleic acid with constant  $\alpha$ -linolenic acid in dietary fats increases (n-3) eicosapentaenoic acid in plasma phospholipids in healthy men. *J. Nutr.* 137: 945-952.
- [20] Garg ML, Wierzbicki AA, Thomson ABR, Clandinin MT. 1988. Dietary cholesterol and/or n-3 fatty acid modulate  $\Delta$ 9-desaturase activity in rat liver microsomes. *Biochim. Biophys. Acta* 962: 330-336.
- [21] Li D, Mann NJ, Sinclair AJ. 1999. Comparison of n-3 polyunsaturated fatty acids from vegetable oils, meat, and fish in raising platelet eicosapentaenoic acid levels in humans. *Lipids* 34: S309.
- [22] Marangoni F, Colombo C, De Angelis L, 2004. Cigarette smoke negatively and dose-dependently affects the biosynthetic pathway of the n-3 polyunsaturated fatty acid series in human mammary epithelial cells. *Lipids* 39: 633-637.
- [23] Phipps, W R, Martini, M C, Lampe, J W, Slavin J L and Kurzer, M S 1993. Effect of flax seed ingestion on the menstrual cycle. *The J. of Clin Endocr & Metab*, 77 (5):1215-1219
- [24] Atkinson, Ch. Lampe, J. W Scholes, D. 2006 Lignan and isoflavone excretion in relation to uterine fibroids: a case-control study of young to middle-aged women in the United States. *Am J Clin Nutr* 84: 587-593
- [25] Sambrook, P.N., Cooper, C., 2006. Osteoporosis *Lancet* 367, 2010-2018.
- [26] Passeri G, Vescovini R, Sansoni P, Galli C, Franceschi C, Passeri M. 2008. Italian Multicentric Study on Centenarians (IMUSCE) Calcium metabolism and vitamin D in the extreme longevity. *Exp Gerontol.* 43: 79-87.
- [27] Burton, J L and Wells, M. 2002. The effect of phytoestrogens on the female genital tract. *J. Clin. Pathol.* 55: 401-407
- [28] Akiyama T, Ishida J, Nakagawa, S. 1987. Genistein, a specific inhibitor of tyrosine-specific protein kinases. *J Biol Chem* 262:5592-5.
- [29] Prasain JK, Arabshahi A, Moore DR 2nd, et al., 2010. Simultaneous determination of 11 phytoestrogens in human serum using a 2 min liquid chromatography/tandem mass spectrometry method. *J Chromatogr B Analyt Technol Biomed Life Sci*; 878: 994-1002.
- [30] Mayer Y, Balbir-Gurman A, Machtei EE. 2009. Anti-tumor necrosis factor- $\alpha$  therapy and periodontal parameters in patients with rheumatoid arthritis. *J Periodontol.* 80: 1414-20.
- [31] Sacco SM, Jiang JM, Reza-López S, et al., 2009. Flaxseed combined with low-dose estrogen therapy preserves bone tissue in ovariectomized rats. *Menopaus.* 16: 545-54.
- [32] McLean, RR. 2009. Proinflammatory cytokines and osteoporosis. *Curr Osteoporos Rep.* 7: 134-9
- [33] Griel, AE, Kris-Etherton, PM, Hilpert, KF, et al., 2007. An increase in dietary n-3 fatty acids decreases a marker of bone resorption in humans. *Nutr J.* 6: 2.
- [34] Kong W, Yen JH, Vassiliou E, Adhikary, S, et al., 2010. Docosahexaenoic acid prevents dendritic cell maturation and in vitro and in vivo expression of the IL-12 cytokine family. *Lipids Health Dis.* 9:12.
- [35] Hala M. Hussein, Madiha M. Abdel-Kader, Seham S. Kasem 2011. Flaxseed down regulates bone resorption in knocked-out ovariectomized rats. *I.J.A.R.*, 3(2):1158-1165
- [36] Jennifer, D.B, Wendy, E.W, Jacqueline, E.L, 2004. 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.* 79: 318-325
- [37] Rodriguez-L.D, Dupasquier, CM, McCullough, R.P., 2010. The cardiovascular effects of flaxseed and its omega-3 fatty acid, alpha-linolenic acid. *Can J Cardiol.* 2010 Nov; 26(9):489-96.
- [38] Mark A. P; Eilis, O; Katarina A., 2004. Dietary Fiber and Risk of Coronary Heart Disease. A Pooled Analysis of Cohort Studies. *Arch Intern Med.*; 164:370-376.
- [39] Gary E. Fraser, U G, Berit L. H, 2007.  $\alpha$ -Linoleic acid, 6-desaturase gene polymorphism, and the risk of nonfatal myocardial infarction. *Am. J. Clin. Nutr.* 85: 554-560.
- [40] Tedgui A. 2005. The role of inflammation in atherothrombosis: implications for clinical practice. *Vasc. Med.* 10: 45-53.

- [41] Leeson C, Mann A, Kattenhorn M ., 2002. Relationship between circulating n-3 fatty acid concentrations and endothelial function in early adulthood. *Eur. Heart J.* 23: 216-222.
- [42] Rallidis LS, Paschos G, Papaioannou ML, 2004. The effect of diet enriched with  $\alpha$ -linolenic acid on soluble cellular adhesion molecules in dyslipidaemic patients. *Atherosclerosis* 174: 127-132
- [43] Mozaffarian, D. and Jason H.Y., 2011 .omega-3 Fatty Acids and Cardiovascular Disease .Effects on Risk Factors, Molecular Pathways, and Clinical Events.*J Am Coll Cardiol.* 58:2047-2067
- [44] Peterson J, Dwyer J, Adlercreutz H, 2010. Dietary lignans: physiology and potential for cardiovascular disease risk reduction.*Nutr Rev.*; 68(10):571-603
- [45] Chantal M. , C. Bassett, R. S. McCullough, A. L. Edel ,2011.The  $\alpha$ -linolenic acid content of flaxseed can prevent the atherogenic effects of dietary trans fat *Am J Physiol Heart Circ Physiol.*, 301: 2220-2226.
- [46] Ueshima H, Stamler J, Elliott P, Chan Q, 2007. Food Omega-3 Fatty Acid Intake of Individuals (Total, Linolenic Acid, Long-Chain) and Their Blood Pressure. (INTERMAP) Study. *Hypertension*; 50(2):313-19.
- [47] 47. Dodin S, Lemay A, Jacques H. 2005. The effects of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women: a randomized, double-blind, wheat germ placebo-controlled clinical trial. *J. Clin. Endocrinol. Metab.* 90: 1390-1397.
- [48] Spence JD, Thornton T, Muir AD, Westcott ND. 2003. The effect of flax seed cultivars with differing content of  $\alpha$ -linolenic acid and lignans on responses to mental stress. *J. Am. Coll. Nutr.* 22: 494-501.
- [49] Jun D, Thomas R. Z, Roberd, M. B., Amita, K. M. , 2010. High habitual dietary  $\alpha$ -linolenic acid intake is associated with decreased plasma soluble interleukin-6 receptor concentrations in male twins. *Am J Clin Nutr.* 92 (1): 177-185
- [50] Kailash P. 2000.Oxidative stress as a mechanism of diabetes in diabetic BB prone rats: Effect of secoisolariciresinol diglucoside (SDG).*Molecular and Cellular Biochemistry* 209: 89-96.
- [51] Cunnane S, Hamadeh MJ, Liede AC, 1995. Nutritional attributes of traditional flaxseed in healthy young adults. *Am J Clin Nutr*; 61:62-8.
- [52] Nestel PJ, Pomeroy SE, Sasahara T,1997. Arterial compliance in obese subjects is improved with dietary plant n $\alpha$ 3 fatty acid from flaxseed oil despite increased LDL oxidizability. *Arterioscler Thromb Vasc Biol.* , 17:1163-70.
- [53] D. Williams, D. W, erhese, LT walker, 2007. 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 and Chemical Toxicology*"45(1):153-159.
- [54] Bergman J M, Thompson LU, Dabrosin C., 2007. 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.*13:1061-1067.
- [55] Chen J, Power KA, Mann J, Cheng A, Thompson LU 2007. Flaxseed alone or in combination with tamoxifen inhibits MCF-7 breast tumor growth in ovariectomized athymic mice with high circulating levels of estrogen. *Exp Biol Med.*; 232:1071-1080.
- [56] Demark-WW, Price DT, Polascik TJ, Robertson CN, Anderson EE, Paulson DF, Walther PJ, Gannon M, Vollmer RT, 2001. Pilot study of dietary fat restriction and flaxseed supplementation in men with prostate cancer before surgery: exploring the effects on hormonal levels, prostate-specific antigen, and histopathologic features. *Urology*; 58:47-52.
- [57] B Miljanovic, K. A. Trivedi, M .R. Dana, 2005. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women *Am J Clin Nutr.* 82:887-893