FLAXSEED IN CARDIOVASCULAR HEALTH AND DISEASE

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Contents

Summary

Flaxseed has been used as food for centuries in many countries especially in Asia. Flaxseed contains 32% to 45% of its mass as oil, of which 51% to 55% is α-linolenic acid (ALA) and 15% to 18% is linoleic acid. CDC-flaxseed is a variety of flaxseed similar to ordinary flaxseed but contains only 2% to 3% of α-linolenic acid. Flax meal does not contain oil and is approximately 55% to 68% of the total mass of flaxseed. Secoisolariciresinol diglucoside (SDG) content of flax meal is 16.4 mg/g. Flax lignan complex (FLC) contains 34% to 38% SDG, 15% to 21% cinnamic acid glucoside, and 9.6% to 11.0% hydroxymethylglutaric acid (HMGA). Both SDG and FLC have been isolated from flaxseed. Lipid lowering effect of flaxseed is variable in experimental animals but it mostly lowers serum lipids in humans. Both flaxseed and CDC-flaxseed have antioxidant and anti-inflammatory activity. Although flaxseed oil possesses anti-inflammatory activity, it does not have lipid lowering effect and antioxidant activity. FLC lowers serum lipid (total cholesterol, LDL-C and triglycerides) but raises serum HDL-C. It is an antioxidant but not an anti-inflammatory agent. SDG is a potent lipid lowering, antioxidant, anti-inflammatory, anti-diabetic and hypotensive agent. Flaxseed and flaxseed oil but not FLC have inhibitory effect on the endothelial cell adhesion molecules. Data on effect of SDG and CDC-flaxseed on cell adhesion molecules are not available. FLC-flaxseed has no effect on monocyte chemo-attract protein-1. Flaxseed oil

(ALA) reduces serum concentrations of monocyte colony stimulating factor. Flaxseed, CDC-flaxseed, FLC, and SDG but not flaxseed oil reduce the formation of foam cells. Flaxseed and SDG have inhibitory effects on certain growth factors but SDG increases the expression of vascular endothelial growth factor in ischemia-reperfusion injury. Flaxseed and flaxseed oil inhibit platelet aggregation. Flaxseed, CDC-flaxseed, FLC, SDG but not flaxseed oil suppresses development of atherosclerosis. High cholesterol diet induces atherosclerosis and regular diet following high cholesterol diet accelerates atherosclerosis. FLC and SDG slow the progression of atherosclerosis. FLC does not regress but SDG induces mild regression of hypercholesterolemic atherosclerosis. There is some concern about the toxic effects of phytic acid, cyanogenic glycosides and cadmium contained in flaxseed, but the amounts are very low to have any toxic effects. Long-term (1 to 4 months) consumption of flaxseed and FLC does not have deleterious effects on hemopoietic system and biochemical markers of liver, and kidney function. Flaxseed and its components have potentials for cardiovascular health benefit but randomized clinical trials have to be performed to determine the efficacy of these agents in primary and secondary prevention of cardiovascular diseases. There is enough evidence for suppression of atherosclerosis in animal model of atherosclerosis. The evidence for slowing and regression of atherosclerosis is limited.

1. Introduction

According to World Health report 2003, cardiovascular deaths world wide are 16.7 million/year or 29.2% of total global death (The Word Health Report, 2003). Of these deaths 7.2 million are due to ischemic heart disease, 5.5 million to cerebrovascular disease and 3.9 million to hypertensive and other cardiac conditions. Heart diseases and stroke are tied to national income (Heart disease and Stroke, 2011). According to the world health organization (WHO) the number of cardiovascular death is projected to increase over 24 million by 2030. Over one million Americans die from myocardial infarction each year (Statistics Canada, 2010). Heart disease and stroke are one of the three leading causes of death in Canada (Rosamond et al., 2008).

Atherosclerosis is the primary cause of the ischemic heart disease. The proximal cause of acute coronary syndrome is thrombosis and the principal underlying cause is atherosclerosis. Over expression of matrix metalloproteinases (MMPs) (Galis et al., 1994) weakens atherosclerotic plaques, causing their rupture (Shah et al., 1995). Plaque rupture and thromboembolism are major causes (90%) of myocardial infarction (Falk et al., 1995), and cerebrovascular disease. There are numerous risk factors for development of atherosclerosis including hyperlipidemia (Ross and Harker, 1976; Castelli, 1988; Prasad and Kalra, 1993) oxidative stress (Steinberg, 1992; Prasad and Kalra, 1993; Prasad et al., 1994; Prasad, 1999; Prasad, 2005), inflammation (Saikku et al., 1988; Prasad, 2000a; Kleemann et al., 2008), hypertension (Alexander, 1995; Prasad, 2000a), diabetes (Colwell et al., 1981; Beckman et al., 2002), smoking (Howard et al., 1998), and obesity (Alexander, 2001; McGill et al., 2002).

The more risk factors one has, the greater are the chances of developing cardiovascular diseases. Modification of risk factors and taking preventive measures would reduce the chances of cardiovascular diseases. For example, every 1% increase in serum cholesterol increases the risk of coronary artery disease (CAD) by 2% to 3%, and

lowering serum cholesterol by 10% reduces CAD risk over 5 years by 50% for men 40 years of age and by 25% for men 60 years of age (Davis et al., 1990). Numerous strategies have been developed to reduce risk factors in an attempt to reduce the development of atherosclerosis and to reduce the chances of developing CAD. Strategies can be developed to reduce the incidence of CAD i.e. prevention by reducing the risk factors. Those who already have CAD and are at risk of recurrence, the strategies should be to slow the progression of and/or regression of atherosclerosis. The drugs that suppress development of atherosclerosis do not necessarily slow progression or regression of atherosclerosis.

This chapter deals with the effectiveness of flaxseed and the components in suppression, slowing of progression and regression of atherosclerosis; in lowering risk factors of atherosclerosis; and in reducing the factors related to the mechanism of development of atherosclerosis.

2. Flaxseed and Its Components

There are two types of flaxseed. One variety, the regular flaxseed contains 32% to 45% of its mass as oil, of which 51% to 55% is α-linolenic acid (ALA) and 15% to 18% is linoleic acid (Oomah and Mazza, 1993). The other variety of flaxseed called CDC-flaxseed has similar oil content (35% of total mass) as regular flaxseed but has only 2% to 3% of ALA. Both types of flaxseed contain similar concentrations of lignan, secoisolariciresinol diglucoside (SDG) (Prasad et al., 1998). Flaxseed is the richest source of SDG (Westcott and Muir, 1998). Flax meal, which is devoid of oil, is approximately 55% – 68% of the total mass of flaxseed, and contains approximately 16.4 mg/g of SDG. The SDG content of flaxseed varies between 0.6 and 1.88 mg/100g (Prasad et al., 1998). SDG in pure form (Westcott and Muir, 1998) and flax lignan complex (FLC) (Westcott and Paton, 2001) have been isolated from flaxseed. FLC, contains 34% – 38% SDG, 15% – 21% cinnamic acid glucoside, and 9.6% – 11.0% hydroxymethylglutaric acid by weight. SDG is metabolized to secoisolariciresinol (SECO), enterodiol (ED) and enterolactone (EL) in the body (Rickard et al., 1996).

3. Pharmacological Activity of Flaxseed and Its Components

Pharmacological activity of flaxseed and its components will be discussed in detail later on in this chapter. However, the activities are briefly summarized in this section.

1. Flaxseed and its components, except flax oil have hypolipidemic effects.
2. They are antioxidant.
3. They have anti-inflammatory effects.
4. Some of them suppress chemokines.
5. Cinnamic acid gluocoside is antioxidant.
6. Hydroxymethylglutaric acid (HMGA) is hypolipidemic agent.
7. Hypotensive.
8. Anti-diabetic.

Flaxseed and Atherosclerosis

This section will comprise of

A. Mechanism of atherosclerosis;
B. Flaxseed and its components on the mechanism of atherosclerosis;
C. Flaxseed and its components on the risk factors for atherosclerosis; and
D. Flaxseed and its components on atherosclerosis.

4. Mechanism of Atherosclerosis

Oxidative hypothesis for development of atherosclerosis is well established. According to this hypothesis, atherosclerosis involves oxidation of low density lipoprotein-cholesterol (LDL-C) and its accumulation in macrophages leading to foam cell formation, the hallmark of initiation of atherosclerosis (Schwartz et al., 1993; Prasad, 2000a). LDL is mildly oxidized to minimally modified LDL (MMLDL) which stimulates smooth muscle and endothelial cells to produce monocyte chemotactic protein-1 (MCP-1). MMLDL also releases macrophage colony stimulating factor (MCSF) from endothelial cells. MMLDL is further oxidized to oxidized LDL (OX-LDL). Expression of various adhesion molecules [endothelial leukocyte adhesion molecules (ELAMs), vascular cell adhesion molecules-1 (VCAM-1), intercellular adhesion molecules-1 (ICAM-1), and soluble ICAM-1 (sICAM-1)] on endothelial cells helps in adherence of monocytes to endothelial cells.

MCP-1 and OX-LDL help in migration of endothelial cell adhered monocytes to subendothelial area. Receptors for LDL are expressed on monocytes but the rate of uptake of native LDL is insufficient to produce foam cells.

Monocyte/macrophage differentiation is facilitated by MCSF. Differentiated macrophage develops receptors for OX-LDL which is taken up by macrophages to form foam cells. Genes expressed in these cells determine the replication of macrophage, and smooth muscle cell replication and migration, T cell replication and chemotaxis of additional monocytes. Numerous growth factors including platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor-β (TGF-β) and cytokines are produced by macrophages (Ross et al., 1990; Falcone et al., 1993). Gene expression and transcription in smooth muscle cells results in the formation of collagen, elastic fiber proteins and growth regulating molecules [bFGF and insulin like growth factor-1 (IGF-1)] (Nilsson et al., 1985). Endothelial cells produce growth promoting molecules (PDGF, bFGF, TGF, IGF-1). MCSF is required for stability and replication of macrophage (Bowen-Pope et al., 1983; DiCorleto, 1984). PDGF and IGF-1 serve as chemo-attractants for smooth muscle cells. bFGF and MCSF, respectively, are chemo-attractant for endothelial cells and macrophages. TGF-β stimulates synthesis of connective tissue and matrix including collagens, proteoglycans and elastic fiber protein (Sporn et al., 1987). Smooth muscle cell proliferation and migration, synthesis of connective tissue and matrix, migration of monocytes, and formation of foam cells results in the development of atherosclerosis.

5. Flaxseed and Its Components on the Mechanisms of Atherosclerosis Development

There are numerous players including, endothelial cells, monocytes, oxygen radicals, adhesion molecules, MCP-1, MCSF, foam cells, smooth muscle cells, growth factors (PDGF, bFGF, TGF-β, IGF-1) and cytokines that are involved in the genesis and maintenance of atherosclerosis. Flaxseed and its components have inhibitory effects on the above players involved in atherosclerosis in order to be effective in suppression, regression and slowing of atherosclerosis. This section assesses the possible effects of flaxseed and its components on the key factors involved in the genesis and maintenance of arthrosclerosis.

5.1. Antioxidant Activity of Flaxseed and Its Components

Regular flaxseed reduced the production of reactive oxygen species (ROS) by polymorphonuclear leukocytes (PMNLs) in normocholesterolemic and hypercholesterolemic rabbits (Prasad, 1997). Flaxseed reduced the $iPF_{2\alpha III F2}$ isoprostane, a measure of lipid proxidation and production of ROS in the endothelium of the lung and alveolar macrophages, and up-regulated the antioxidant enzyme hemoxygenase-1 in pulmonary ischemia-reperfusion injury (Lee et al., 2008). Flaxseed has been shown to prevent the carbon tetrachloride-induced decreases in the antioxidant enzymes [superoxide dismutase (SOD), catalase, and glutathione peroxidise (GSHPx)] in rat liver (Rajesha et al., 2006). The antioxidant activity of CDC flaxseed has not been reported. SDG scavenges hydroxyl radicals (·OH) (Prasad, 1997a). The antioxidant activity of SDG was measured using chemiluminescent activity of PMNLs (PMNL-CL) by Prasad (2000). Activated PMNLs produce ROS such as superoxide anion (O_2^-), H_2O_2, ·OH and singlet oxygen ($^1O_2^-$), which is measured as chemiluminescent activity (PMNL-CL). Prasad (2000) reported that SDG in a concentration-dependent manner reduced the PMNL-CL, suggesting that SDG has antioxidant activity. The antioxidant activity of SDG was 1.27 times greater than vitamin E. All these metabolites (SECO, ED, EL) have antioxidant activity. SECO, ED, and EL were respectively 3.83, 3.95, and 3.45 times more potent than SDG as antioxidant.

FLC reduces the lipid peroxidation product malondialdehyde, a measure of oxidative stress, in aorta and serum of hypercholesterolemic rabbits (Prasad, 2005). FLC increases the antioxidant reserve in hypercholesterolemic rabbit aorta.

Flax oil had no effect on serum or aortic MDA, and antioxidant reserve of aorta, but reduced the generation of ROS by white blood cells in hypercholesterolemic rabbits (Lee and Prasad, 2003). Flax oil increased the lipid peroxidation product in liver, heart and aortic tissue of rats and this effect was associated with reduction in SOD (L'Abbé et al., 1991). Flax oil elevated the activity of catalase and GSHPx in rats (Ramaprasad et al., 2005). However flax oil, in other study, has no effect on the activity of SOD and catalase in liver of monkey in vivo and in vitro (Kaasgaard et al., 1992).

The data suggest that all components of flaxseed have antioxidant activity but the activity with SDG is consistent. The antioxidant activity of flaxseed, CDC-flaxseed, FLC is importantly due to the SDG content in these agents.

5.2 Flaxseed and Its Components on Inflammatory Mediators

Inflammation is involved in the atherosclerosis (Libby et al., 2002). Proinflammatory cytokines increase the expression of chemokines and adhesion molecules (Libby et al., 2002). The effects of flaxseed on cytokines are contradictory. Flaxseed reduces the expression of interleukin-6 (IL-6) and VCAM-1 in aortic tissue of hypercholesterolemic LDL receptor deficient ($LDLR^{-/-}$) and normocholesterolemic mice (Dupasquier et al., 2007). Flaxseed inhibited the release of tumor necrosis factor-alpha (TNF-α), IL-1β and IL-6 (Tetta et al., 1990). However flaxseed in one other study did not lower serum levels of TNF-α and IL-6, in overweight and hypertensive people with a family history of diabetes (Rhee and Brunt, 2011). Flaxseed had no effect on serum levels of high sensitivity c-reactive protein (hs-CRP) in overweight and hypertensive people with a family history of diabetes (Rhee and Brunt, 2011), and in hypercholesterolemic men and post-menopausal women (Bloedon et al., 2008). There are no data on the effect of CDC-flaxseed and SDG on the inflammatory mediators.

Consumption of FLC (543 mg/day) for six months did not alter the serum levels of TNF-α and IL-6 in a randomized double-blind placebo-controlled study in healthy subjects (Cornish et al., 2009). Hallund et al. (2008) also reported that FLC (500 mg/day) given for six months to healthy post-menopausal women had no effect on serum TNF-α and IL-6.

The effects of flaxseed oil on inflammatory mediators are variable. Flaxseed oil consumption in healthy individuals reduced the production of TNF-α and IL-1β by mononuclear cells in humans (Caughey et al., 1996), and serum levels of IL-6 in dyslipidemic men (Bemelmans, 2004). However in a well controlled trial in healthy abdominally obese adult males and females, flaxseed did not alter the serum levels of TNF-α and IL-6 (Nelson et al., 2007). ALA (2 g/day) for twelve weeks did not alter the production of TNF-α, IL-1β and IL-6 (Thies et al., 2001). Consumption of ALA (3.5 g/day) for twelve weeks also did not alter the production of TNF-α, IL-1β, IL-2, IL-4, IL-10 and interferon-gamma (INF-γ) in healthy humans (Wallace et al., 2003). However ALA (12 g/day or greater) reduced the serum levels of cytokines. ALA (14 g/day) for four weeks reduced the production of TNF-α and IL-1β by mononuclear cells in humans (Caughey et al., 1996).

Flaxseed oil lowers serum hs-CRP in dyslipidemic males (Caughey et al., 1996). Lowering of hs-CRP with 15 mL of flaxseed oil/day for 12 weeks (Paschos et al., 2005) and for six weeks (Zhao et al., 2004), has also been reported in humans. ALA (8.1 g/day) decreased the hs-CRP in dyslipidemic patients (Paschos et al., 2004). It appears that ALA is effective in lowering the serum levels of hs-CRP. Flaxseed (40 g/day) for twelve weeks did not lower hs-CRP in a randomized cross-over design in overweight hypertensive people with family history of diabetes (Rhee and Brunt, 2011).

In a randomized double-blind controlled clinical trial in hypercholesterolemic men and post-menopausal women, flaxseed (40 g/day) for ten weeks was ineffective in lowering the serum levels of hs-CRP (Bloedon et al., 2008). Rhee and Brunt (2011) also reported that flaxseed (40 g/day) for twelve weeks did not lower serum hs-CRP. FLC in the dose

of 500 mg/day SDG equivalent for six weeks reduced the serum levels of CRP in healthy post-menopausal women (Cornish et al., 2009).

5.3. Flaxseed and Components, Chemokines and Cell Adhesion Molecules

Cell adhesion molecules are involved in the adherence of monocytes to the endothelial cell and chemokines are involved in the migration of monocytes to subendothelial surface. Inhibition of these agents would suppress the development of atherosclerosis.

Flaxseed reduced the expression of VCAM-1 in aortic tissue of hypercholesterolemic $LDLR^{-/-}$ mice but did not alter the expression of VCAM-1 in aortic tissue of normocholesterolemic mice (Dupasquier et al., 2007). Flaxseed oil (15 ml/day) for 12 weeks reduced the serum sVCAM-1 but had not effect on the levels of sICAM-1 and sE-selectin in dyslipidemic patients (Rallidis et al., 2004). Consumption of ALA (2 g/day) for 12 weeks reduced the serum levels of sVCAM-1 and sE-selectin but had no the levels of sICAM-1 in healthy adults (Thies et al., 2001). They also reported that consumption of ALA (2 g/day) for 12 weeks reduced the monocyte activated release of sVCAM-1 and sE-selectin but had no effect on the release of sVCAM-1.

Consumption of FLC in the dose of 500 mg/day SDG equivalent for 6 weeks had no effect on the serum levels of sICAM-1 and sVCAM-1 in healthy post-menopausal women (Hallund et al., 2008). No data are available on the effects of CDC-flaxseed and SDG on cell adhesion molecules. The data on cell adhesion molecules for flaxseed, flax oil and FLC suggest that their effects are variable on cell adhesion molecules.

FLC (500 mg/day SDG equivalent) had no effect on the MCP-1 in healthy post-menopausal women (Hallund et al., 2008).

5.4. Flaxseed Components and Monocyte Colony Stimulating Factor (MCSF) and Foam Cells

As stated in the section on the mechanism of atherosclerosis, MCSF helps in maturation of monocyte to macrophage which then develops receptors for uptake of OX-LDL resulting in foam cell formation. Inhibition of expression of MCSF and formation of foam cells would reduce/prevent the development of atherosclerosis. Consumption of flaxseed oil (15 ml/day) for 12 weeks reduced the serum levels of MCSF in dyslipidemic patients (Paschos et al., 2005). ALA in the dose of 8.1 g/day for 12 weeks reduced the MCSF concentration in serum of dyslipidemic patients (Paschos et al., 2004). Flaxseed, flax lignan complex, CDC-flaxseed and SDG but not flax oil reduced the formation of foam cells (Prasad et al., 1998; Prasad, 1999; Lee and Prasad, 2003; Prasad, 2005).

5.5. Flaxseed Components and Growth Factors

Growth factors such as PDGF, bFGF, TGF-β and IGF-1 play an important role in the development of atherosclerosis. This section deals with the effects of flaxseed and its components on the growth factors. Both flaxseed and SDG inhibit the epidermal growth factor receptor and insulin-like growth factor receptor (Chen et al., 2009). They also

reduce the plasma levels of IGF-1 in rat (Rickard et al., 2000). However, SDG has been reported to increase the protein expression of vascular endothelial growth factor (VEGF) in ischemia-reperfusion injury model of rat (Penumathsa et al., 2008) and of human coronary arteriolar endothelial cells (HCAEC) (Penumathsa et al., 2007). Dietary flaxseed inhibits the expression of proliferating cell nuclear antigen (PCNA) (Dupasquier et al., 2007).

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Bibliography

Alexander JK. (2001). Obesity and coronary heart disease. *Am J Med Sci*, 321, 215-224.[This paper reports the role of obesity in coronary heart disease].

Alexander RW. (1995). Hypertension and the pathogenesis of atherosclerosis. Oxidative stress and the mediation of arterial inflammatory response: a new perspective. *Hypertension*, 25, 155-161.[This paper reports the role of hypertension mediated oxidative stress and inflammation in pathophysiology of atherosclerosis].

Allman MA, Pena MM, Pang D. (1995). Supplementation with flaxseed oil versus sunflower seed oil in healthy young men consuming a low fat diet: effects on platelet composition and function. *Eur J Clin Nutr*, 49, 169-178.[This paper repots the effects of flaxseed oil and sunflower seed oil platelet composiyion and function].

Bassett CM, Edel Al, Patenaude AF, McCullough RS, Blackword DP, Chouinard PY, Pquin P, Pierce GN. (2010). Dietary vaccenic acid has antiatherogenic effects in LDLR$^{-/-}$ mice. *J Nutr*, 140, 18-24.[This paper reports the anti-atherosclerotic effect of vaccenic acid].

Bassett CM, McCullough RS, Adel AL, Maddford TG, Dibror E, Blackword DP, Austria JA, Pierce GN. (2009). Trans-fatty acids in the diet stimulate atherosclerosis. *Metabolism*, 58, 1802-1808. [This paper reports that trans-fatty acids is atherogenic].

Beckman JA, Creager MA, Libby P. (2002). Diabetes and atherosclerosis; epidemiology, pathophysiology, and management. *JAMA*, 287, 2570-2581.[This is a review paper describing the epidemiology, pathophysiology and management of atherosclerosis in diabetes].

Bemelmans WJ, Lefrandt JD, Feskens EJ, et al. (2004). Increased alpha-linolenic acid intake lowers C-reactive protein, but has no effect on markers of atherosclerosis. *Eur J Clin Nutr*, 58, 1083-1089.[Alpha-linolenic acid lowers c-reactive protein].

Berry EM, Hirsch J. (1986). Does dietary linolenic acid influence blood pressure? *Am J Clin Nutr*, 44, 336-340.[1% increase in the alpha-linolenic acid content of adipose tissue decreases arterial pressures].

Bierenbaum ML, Reichstein R, Watkins TR, et al. (1993). Reducing atherogenic risk in hyperlipemic humans with flax seed supplementation: a preliminary report. *J Am Coll Nutr*, 12, 501-504.[Flax seed reduces the development of atherosclerosis in humans with hypercholesterolemia].

Bloedon LT, Balikai S, Chittams J, et al. (2008). Flaxseed and cardiovascular risk factors: results from a double blind, randomized, controlled clinical trial. *J Am Coll Nutr*, 27, 65-74.[Flaxseed does not reduce the serum levels of c-reactive protein in hypercholesterolemic men and post-menopausal women].

Bowen-Pope DF, Dicorleto PE, Ross R. (1983). Interactions between the receptors for platelet-derived growth factor and epidermal growth factor. *J Cell Biol*, 96, 679-683.[This paper describes the interaction between receptors for platelet –derived growth factor and epidermal growth factor].

Butler GW, Conn EE. (1964). Biosynthesis of the cyanogenic glucosides linamarin and lotaustralin. I. Labeling studies in vivo with Linum usitatissimum. *J Biol Chem*, 239, 1674-1679.[This paper reports the biosynthesis of cyanogenic glycosides].

Castelli WP. (1988). Cholesterol and lipids in the risk of coronary artery disease- the Framingham Heart Study. *Can J Cardiol*, 4, Suppl A:5A-10A.[Cholesterol and lipids are risk factors for coronary artery disease].

Caughey GE, Mantzioris E, Gibson RA, et al. (1996). The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. *Am J Clin Nutr*, 63, 116-122.[Flaxseed oil reduces the production of TNF-alpha and interleukin-1beta in human mononuclear cells].

Chantall M, Bassett CM, McCullough RS, Edel AL, Patnaude PA, Lavallee RK Pierce GN. (2011). The α-linolenic acid content of flaxseed can prevent atherogenic effects of dietary trans fat. *Am J Physiol Heart Circ Physiol*, 301, H2220-H2226. [Alpha-linolenic acid from flaxseed prevents trans-fatty acid –induced atherosclerosis].

Chen J, Saggar JK, Corey P, Thompson LU. (2009). Flaxseed and pure secoisolariciresinol diglucoside, but not flaxseed hull, reduce human breast tumor growth (MCF-7) in athymic mice. *J Nutr*, 139, 2061-2066. [Flaxseed and secoisolariciresinol diglucoside reduces human breast cancer growth].

Colwell JA, Lopes-Virella M, Halushka PV. (1981). Pathogenesis of atherosclerosis in diabetes mellitus. *Diabetes Care*, 4, 121-133. [Mechanisms of development of atherosclerosis in diabetes mellitus hs been described in this paper].

Cornish SM, Chilibeck PD, Paus-Jennsen L, et al. (2009). A randomized controlled trial of the effects of flaxseed lignan complex on metabolic syndrome composite score and bone mineral in older adults. *Appl Physiol Nutr Metab*, 34, 89-98. [Flax lignin complex does alter the serum levels of TNF-alpha and Interleukin-6 in healthy subjects].

Cunnane SC, Ganguli S, Menard C, et al. (1993). High alpha-linolenic acid flaxseed (Linum usitatissimum): some nutritional properties in humans. *Br J Nutr*, 69, 443-453. [Flaxseed reduces total cholesterol and low density lipoprotein cholesterol but has no effect on high density lipoprotein cholesterol in healthy subjects].

Daun JK, Przybylski R. (2000). Effects of environment as determined by oil content and unsaturation on the composition of flaxseed. INFORM Abstracts, 91st AOCS Annual Meeting & Expo. San Diego, CA. April 25-28, 11, 106. [Oil content of flaxseed depends upon environment].

Davis HR, Bridenstine RT, Vesselinovitch D, et al. (1987). Fish oil inhibits development of atherosclerosis in rhesus monkeys. *Arteriosclerosis*, 7, 441-444.[Fish oil reduces the development of atherosclerosis].

Davis C, Rifkind B, Brenner H, et al. (1990). A single cholesterol measurement underestimates the risk of coronary heart disease. An empirical example from the Lipid Research Clinics Mortality Follow-up Study. *JAMA*, 264, 3044-3046.[A single measurement of serum cholesterol underestimates the risk of coronary artery disease].

DiCorleto PE. (1984). Cultured endothelial cells produce multiple growth factors for connective tissue cells. Exp Cell Res, 153, 167-172.[Growth factors for connective tissue cells are produced by cultured endothelial cells].

Dodin S, Cunnane SC, Mâsse B, et al. (2008). Flaxseed on cardiovascular disease markers in healthy menopausal women: a randomized, double-blind, placebo-controlled trial. *Nutrition*, 24, 23-30. [Flaxseed reduces LDL peak particle size and increases apolipoprotein A-1 and B in healthy menopausal women].

Dodin S, Lemay A, Jacques H, Légaré F, Forest JC, Mâsse B. (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. [Flaxseed reduces serum TC and HDL-C in menopausal women].

Dupasquier CM, Dibrov E, Kneesh A, et al. (2007). Dietary flaxseed inhibits atherosclerosis in the LDL receptor-deficient mouse in part through antiproliferative and anti-inflammatory actions. *Am J Physiol Heart Circ Physiol*, 293, H2394-402. [Flaxseed reduces the development of atherosclerosis in LDL receptor deficient mice through inhibition of expression of proliferating cell nuclear antigen and reduction of TC].

Dupasquier CM, Weber AM, Ander BP, et al. (2006). Effects of dietary flaxseed on vascular contractile function and atherosclerosis during prolonged hypercholesterolemia in rabbits. *Am J Physiol Heart Circ Physiol*, 291, H2987-96.[Flaxseed reduced hypercholesterolemic atherosclerosis in aorta and coronary artery of rabbit].

Falcone DJ, McCaffrey TA, Haimovitz-Friedman A, Vergilio JA, Nicholson AC. (1993). Macrophage and foam cell release of matrix-bound growth factors. Role of plasminogen activation. *J Biol Chem*, 268, 11951-11958.[Macrophage-derived foam cells releases TGF-beta and bFGF from extracellular matrix .[This provides mechanism by which macrophage and foam cells can stimulate atherosclerosis].

Falk E, Shah PK, Fuster V. (1995). Coronary plaque disruption. *Circulation*, 92, 657-671.[This paper reviews the mechanism of rupture of coronary plaque].

Freese R, Mutanen M, Valsta LM, et al. (1994). Comparison of the effects of two diets rich in monounsaturated fatty acids differing in their linoleic/alpha-linolenic acid ratio on platelet aggregation. *Thromb Haemost*, 71, 73-77. [Flaxseed oil reduces platelet aggregation in healthy men].

Fukumitsu S, Aida K, Ueno N, et al. (2008). Flaxseed lignan attenuates high-fat diet-induced fat accumulation and induces adiponectin expression in mice. *Br J Nutr*, 100, 669-676.[Flax lignan induces adiponectin expression and reduces high fat diet-induced fat accumulation].

Galis ZS, Sukhova GK, Lark MW, Libby P. (1994). Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. *J Clin Invest*, 94, 2493-2503.[Vulnerable atherosclerosclerotic plaques shows increased expression of matrix metalloproteinase and matrix degradation].

Gann PH, Hennekens CH, Sacks FM, et al. (1994). Prospective study of plasma fatty acids and risk of prostate cancer. *J Natl Cancer Inst*, 86, 281-286.[Flaxseed oil consumption increases the risk of developing prostate cancer].

Giovannucci E, Rimm EB, Colditz GA, et al. (1993). A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst*, 85, 1571-1579. .[Flaxseed oil consumption increases the risk of developing prostate cancer].

Haliga R, Mocanu V, Oboroceanu T, et al. (2007). The effects of dietary flaxseed supplementation on lipid metabolism in streptozotocin-induced diabetic hamsters. *Rev Med Chir Soc Med Nat Iaşi*, 111, 472-426.[Flaxseed reduces TC and increases HDL-C].

Hallund J, Ravn-Haren G, Bügel S, Tholstrup T, Tetens I. (2006). A lignan complex isolated from flaxseed does not affect plasma lipid concentrations or antioxidant capacity in healthy postmenopausal women. *J Nutr*, 136,112-116.[Flax lignan complex does not affect serum lipids or antioxidant activity in postmenopausal women].

Hallund J, Tetens I, Bügel S, Tholstrup T, Bruun JM. (2008). The effect of a lignan complex isolated from flaxseed on inflammation markers in healthy postmenopausal women. *Nutr Metab Cardiovasc Dis*, 18, 497-502.[Flax lignin complex does notaffect serum TNF-alpha and IL-6].

Hallund J, Tetens I, Bügel S, Tholstrup T, Ferrari M, Teerlink T, Kjaer A, Wineberg N. (2006). Daily consumption for six weeksof a lignan complex isolated from flaxsees does not affect endothelial function in healthy postmenopausal women. *J Nutr*, 136, 2314-2318.[Flax lignan complex does not affect endothelial cell function].

Harvei S, Bjerve KS, Tretli S, et al. (1997). Prediagnostic level of fatty acids in serum phospholipids: omega-3 and omega-6 fatty acids and the risk of prostate cancer. *Int J Cancer*, 71, 545-551.[Omega-3 and omega-6 fatty acids increase the risk of prostate cancer].

Heart disease and stroke worldwide tied to national income. *Science Daily*, July 8, 2011.[Heart disease and stroke are tied to national income].

Howard G, Wagenknecht LE, Burke GL, Diez-Roux A, Evans GW, Mcgovern P, Nieto FJ, Tell GS. (1998). Cigarette smoking and progression of atherosclerosis: the atherosclerosis risk in communities (ARIC) study. *JAMA*, 279, 119-124.[Cigarette smoking increases progression of atherosclerosis].

Kaasgaard SG, Hølmer SG, Høy CE, et al. (1992). Effects of dietary linseed oil and marine oil on lipid peroxidation in monkey liver in vivo and in vitro. *Lipids*, 27, 740-745. [Flaxseed oil has no effect on the activity of SOD and catalase in liver of monkey in vivo and in vitro].

Kelley DS, Nelson GJ, Love JE, et al. (1993). Dietary alpha-linolenic acid alters tissue fatty acid composition, but not blood lipids, lipoproteins or coagulation status in humans. *Lipids*, 28, 533-537.[Flaxseed oil did not alter the serum TG, TC,HDL-C, LDL-C, apolipoprotein A-1, and apolipoprotein B, nor has any effect on bleeding time, prothrombin time and partial prothrombin time. It ,however, increased the alpha-linolenic acid content of serum and mononuclear cells in blood].

Kestin M, Clifton P, Belling GB, et al. (1990). n-3 fatty acids of marine origin lower systolic blood pressure and triglycerides but raise LDL cholesterol compared with n-3 and n-6 fatty acids from plants. *Am J Clin Nutr*, 51, 1028-1034.[Marine based n-3 fatty acids lower systolic blood pressure and TG but increases LDL-C].

Kleemann R, Zadelaar S, Kooistra T. (2008). Cytokines and atherosclerosis: a comprehensive review of studies in mice. *Cardiovasc Res*, 79, 360-366.[This is a review on the role of cytokines in atherosclerosis].

Kritchevsky D, Tepper SA, Klurfeld DM. (1991). Influence of flaxseed on serum and liver lipids in rats. *J Nutr Biochem*, 2, 133-134.[Flaxseed reduces the serum levels of TC and LDL-C without any effect on serum TG in rat].

L'Abbé MR, Trick KD, Beare-Rogers JL. (1991). Dietary (n-3) fatty acids affect rat heart, liver and aorta protective enzyme activities and lipid peroxidation. *J Nutr*, 121, 1331-1340.[Flaxseed oil increases lipid peroxidation product in liver, heart and aortic tissue and this effect is associated with reduction in superoxide enzyme].

Lee JC, Bhora F, Sun J, et al. (2008). Dietary flaxseed enhances antioxidant defenses and is protective in a mouse model of lung ischemia-reperfusion injury. *Am J Physiol Lung Cell Mol Physiol*, 294, L255-L265.[Flaxseed increases antioxidant defense mechanism in lung ischemia-reperfusion injury].

Lee P, Prasad K. (2003). Effects of flaxseed oil on serum lipids and atherosclerosis in hypercholesterolemic rabbits. *J Cardiovasc Pharmacol Therapeut*, 8, 227-235.[flaxseed oil has no effect on serum lipids and atherosclerosis].

Li D, Sinclair A, Wilson A, et al. (1999). Effect of dietary alpha-linolenic acid on thrombotic risk factors in vegetarian men. *Am J Clin Nutr*, 69, 872-882.[flaxseed oil has no antiplatelet activity in vegetarian men].

Libby P, Ridker PM, Maseri A. (2002). Inflammation and Atherosclerosis. *Circulation*, 105, 1135-1143.[This paper describes the role of inflammation in atherosclerosis].

Likhodii SS, Musa K, Mendonca A, Dell C, Burnham WM, Cunnane SC. (2000). Dietary fat, ketosis, and seizure resistance in rats on ketogenic diet. *Epilepsia*, 41, 1400-1410.[Ketogenic diet does not protect seizure in rats].

Lucas A, Lightfoot SA, Hammond LJ, et al. (2004). Flaxseed reduces plasma cholesterol and atherosclerotic lesion formation in ovariectomized Golden Syrian hamsters. *Atherosclerosis*, 173, 223-229.[Flaxseed reduces TC and atherosclerosis ,increases TG and has no effect on HDL-C].

Mandaşescu S, Mocanu V, Dascaliţa AM, et al. (2005). Flaxseed supplementation in hyperlipidemic patients. *Rev Med Chir Soc Med Nat Iaşi*, 109, 502-206.[Flaxseed reduces TC,LDL-C and TC/HDL-C ,increases TG but has no effect on HDL-C].

McGill HC Jr, Mcmahan CA, Herderick EE, Zieske AW, Malcoln GT, Tracy RE, Strong JP. (2002). Obesity accelerates the progression of coronary atherosclerosis in young men. *Circulation*, 105, 2712-2718.[Obesity increases progression of coronary atherosclerosis].

Morris D. (2000). Cyanogenic glycosides in flaxseed: implications for the health of North Americans. Winnipeg, MB, Canada. Flax Council of Canada.[Flaxseed continscyanogenic glycosides which have health implication].

Nelson TL, Stevens JR, Hickey MS. (2007). Inflammatory markers are not altered by an eight week dietary α-linolenic acid intervention in healthy abdominally obese adult males and females. *Cytokine*, 38, 101-106.[Dietary alpha-linolenic acid has no effect on inflammatory markers].

Nestel PJ, Pomeroy SE, Sasahara T, et al. (1997). 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*, 17, 1163-1170.[Flaxseed oil has no effect on arterial pressure].

Nilsson J, Sjölund M, Palmberg L, Thyberg J, Heldin CH. (1985). Arterial smooth muscle cells in primary culture produce a platelet-derived growth factor-like protein. *Proc Natl Acad Sci USA*, 82, 4418-4422.[Modulation of Primary cell culture of arterial smooth muscle produces platelet-derived growth factor- like protein].

Nordstrom DC, Honkanen VE, Nasu Y, Antila E, Friman C, Konttinen YT. (1995). Alpha-linolenic acid in the treatment of rheumatoid arthritis. A double-blind, placebo-controlled and randomized study; flaxseed vs. safflower seed. *Rheumatol Int*, 14, 231-234.[Alpha-linolenic acid does not improve rheumatoid arthritis].

Oomah BD, Konaschuk EO, Mazza G. (1996). Phytic acid content of flaxseed as influenced by cultivar, growing season and location. *J Agric Food Chem*, 44, 2663-2666.[Phytic acid content of flaxseed is dependent upon cultivar, growing season and location].

Oomah BD, Mazza G. (1993). Flaxseed proteins: A review. *Food Chem*, 48, 109-114.[Flaxseed contains 32%to 45% of its mass as oil, of which 51% to55% is alpha-linolenic acid and 15% to 18% is linoleic acid].

Pan A, Sun J, Chen J, Ye X, Li H, et al. (2007). Effects of a flaxseed-derived supplement in type-2 diabetic patients: a randomized, double-blind, crossover trial. *PLoS One*, 2(11): e1148(1-7).[Flax-derived lignan improved glycemic control as measured by hemoglobin A1c].

Paschos GK, Magkos F, Panagiotakos DB, Votteas V, Zampelas A. (2007). Dietary supplementation with flaxseed oil lowers blood pressure in dyslipidemic patients. *Eur J Clin Nutr*, 61, 1201-1206.[Dietary supplementation with flaxseed oilreduces arterial pressure in dyslipidemic patients].

Paschos G, Rallidis LS, Liakos GK, et al. (2004). Background diet influences the anti-inflammatory effect of alpha-linolenic acid in dyslipidaemic patients. *Br J Nutr*, 92, 649-655.[Flaxseed oil lowers serum levels of inflammatory markers more profoundly when the background diet is rich in saturated fatty acids and poor in mono-saturated fatty acid].

Paschos GK, Yiannakouris N, Rallidis LS, et al. (2005). Apolipoprotein E genotype in dyslipidemic patients and response of blood lipids and inflammatory markers to alpha-linolenic acid. Angiology, 56, 49-60.[Flaxseed oil lowers the serum levels of high sensitivity C-reactive protein].

Paschos GK, Zampelas A, Panagiotakis DB, et al. (2007a). Effects of flaxseed oil supplementation on plasma adiponectin levels in dyslipidemic men. *Eur J Nutr*, 46, 315-320.[Flaxseed oil has no effect on the plasma levels of adiponectin in dyislipidemic men].

Patade A, Devareddy L, Lucas EA, et al. (2008). Flaxseed reduces total and LDL cholesterol concentrations in Native American postmenopausal women. *J Women's Health*, 17, 355-366.[Flaxseed reduces the serum levels of TC and LDLC].

Penumathsa SV, Koneru S, Thirunavukkarasu M, et al. (2007). Secoisolariciresinol diglucoside: relevance to angiogenesis and cardioprotection against ischemia-reperfusion injury. *J Pharmacol Exp Ther*, 320, 951-959.[Secoisolariciresinol diglucoside has a potent angiogenic and antiapoptotic properties that may contribute to its cardioprotective effect in ischemic model].

Penumathsa SV, Koneru S, Zhan L, et al. (2008). Secoisolariciresinol diglucoside induces neovascularization-mediated cardioprotection against ischemia-reperfusion injury in hypercholesterolemic myocardium. *J Mol Cell Cardiol*, 44, 170-179.[Secoisolariciresinol diglucoside reduces ventricular remodeling by neovascularization of infarcted hypercholesterolemic myocardium].

Prasad K. (2009). Flax lignan complex slows down the progression of atherosclerosis in hyperlipidemic rabbits. *J Cardiovasc Pharmacol Ther*, 14, 38-48.[Flax lignin complex slows the progression of hypercholesterolemia- induced atherosclerosis].

Prasad K. (2009a). Vitamin E does not regress hypercholesterolemic atherosclerosis. *J Cardiovasc Pharmacol Ther*, 14, 231-241.[Vitamin E does not regress atherosclerosis].

Prasad K. (2009b). Vitamin E does not slow the progression of hypercholesterolemic atherosclerosis. *Int J Angiol*, 18, 89-95.[Vitamin E does not slow progression of atherosclerosis].

Prasad K. (2008). Regression of hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinol diglucoside isolated from flaxseed. *Atherosclerosis*, 197, 34-42.[Treatment with secoisolariciresinol diglucoside for shorter duration does not regress but for longer duration regresses hypercholesterolemic atherosclerosis].

Prasad K. (2008a). Serum biochemical changes in rabbits on regular diet with or without flax lignan complex following a high cholesterol diet. *Int J Angiol*, 17, 27-32.[Flax lignan complex has no effect on on serum electrolytes and enzymes related to liver function and biochemical parameters related to kidney function].

Prasad K. (2007). A study on regression of hypercholesterolemic atherosclerosis in rabbits by flax lignan complex. *J Cardiovasc Pharmacol Ther*, 12, 304-313.[Flax lignin complex does not regress atherosclerosis].

Prasad K. (2005). Hypocholesterolemic and antiatherosclerotic effect of flax lignan complex isolated from flaxseed. *Atherosclerosis*, 179, 269-275.[Flax lignin complex lowers serum levels of TC, LDL-C, TC/HDL-C, MDA of serum and aorta, and suppresses hypercholesterolemic atherosclerosis].

Prasad K. (2005a). Effect of chronic administration of lignan complex isolated from flaxseed on the hemopoietic system. *Mol Cell Biochem*, 270, 139-145.[Flax lignin complex has no effect on hemopoietic system].

Prasad K. (2004). Antihypertensive activity of secoisolariciresinol diglucoside (SDG) isolated from flaxseed: Role of guanylate cyclase. *Int J Angiol*, 13, 7-14.[Secoisolariciresinol diglucoside lowers blood pressure(systolic, diastolic and mean)].

Prasad K. (2002). Suppression of phosphoenolpyruvate carboxykinase gene expression by secoisolariciresinol diglucoside (SDG), a new antidiabetic agent. *Int J Angiol*, 11, 107-109.[.Secoisolariciresinol diglucoside suppresses the expression of phosphoenolpyruvate carboxykinase gene , a rate limiting step in gluconeogenesis].

Prasad K. (2001). Secoisolariciresinol diglucoside from flaxseed delays the development of type-2 diabetes in Zucker rat. *J Lab Clin Med*, 138, 32-39.[Secoisolariciresinol diglucoside delays the development of type-2 diabetes in Zucker rats].

Prasad K. (2000). Antioxidant activity of secoisolariciresinol diglucoside-derived metabolites, secoisolariciresinol, enterodiol, and enterolactone. Int J Angiol, 9, 220-225.[Metabolites of secoisolariciresinol diglucoside are antioxidans].

Prasad K. (2000a). Pathophysiology of atherosclerosis. In: *Textbook of Angiology*, Eds. JB Chang, R Olsen, K Prasad and BE Sumpio, 85-105. Springer-Verlag New York, Inc.[This chapter of the book describes the pathophysiology of atherosclerosis in detail].

Prasad K. (2000b). Oxidative stress as a mechanism of diabetes in diabetic BB prone rats: effects of secoisolariciresinol diglucoside (SDG). *Mol Cell Biochem*, 209, 89-96.[This paper reports that type-1 diabetes is associated with increased oxidative stress and that secoisolariciresinol diglucoside reduces the incidence of this type of diabetes and this effect is associated with reduction in oxidative stress].

Prasad K. (1999). Reduction of serum cholesterol and hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinol diglucoside (SDG) isolated from flaxseed. *Circulation*, 99, 1355-1362.[Secoisolariciresinol diglucoside reduces the serum levels of TC, LDL-C,TC/HDL-C, oxidative stress and development of atherosclerosis].

Prasad K. (1997). Dietary flaxseed in prevention of hypercholesterolemic atherosclerosis. *Atherosclerosis*, 132, 69-76.[Dietary flaxseed reduces the development of atherosclerosis, oxygen radical producing activity of polymorphonuclear leucocytes and serum levels of TC].

Prasad K. (1997a). Hydroxyl radical-scavenging property of secoisolariciresinol diglucoside (SDG) isolated from flaxseed. *Mol Cell Biochem*, 168, 117-123.[Secoisolariciresinol diglucoside scavenges hydroxyl radical].

Prasad K, Kalra J. (1993). Oxygen free radicals and hypercholesterolemic atherosclerosis: effect of vitamin E. *Am Heart J*, 125, 958-973.[This paper reports that hypercholesterolemic atherosclerosis is associated with increased oxidative stress and that vitamin E suppresses the athersclerosis without affecting serum cholesterol. Supression of atherosclerosis is associated with reduction in reduction in oxidative stress].

Prasad K, Kalra J, Lee P. (1994). Oxygen free radicals as a mechanism of hypercholesterolemic atherosclerosis: effects of probucol. *Int J Angiol*, 3, 100-112.[This paper reports that hypercholesterolemic atherosclerosis is associated with an increase in oxidative stress and that probucol reduces the development of atherosclerosis which is associated with a decrease in oxidative stress].

Prasad K, Mantha SV, Muir AD, et al. (1998). Reduction of hypercholesterolemic atherosclerosis by CDC-flaxseed with very low alpha-linolenic acid. *Atherosclerosis*, 136, 367-375.[CDC-flaxseed reduces the development of hypercholesterolemic atherosclerosis and this effect is associated with decreases in serum TC, LDL-C and TC/HDL-C, increases in serum TG and VLDL-C, and unaltered serum HDL-C].

Prasad K, Mantha SV, Muir AD, Westcott ND. (2000). Protective effect of secoisolariresinol diglucoside against stretozotocin-induced diabetes and its mechanisms. *Mol Cell Biochem*, 206, 141-149.[Streptozotocin- induced diabetes is associated with increases in serum and pancreatic malondealdehyde, and oxygen radical generation by white blood cells , and decreases in antioxidant reserve in pancreas].

Rajesha J, Murthy KN, Kumar MK, Madhusudhan B, Ravishankar GA. (2006). Antioxidant potentials of flaxseed by in vivo model. *J Agric Food Chem*, 54, 3794-3799.[Flaxseed prevents the carbon tetrachloride- induced decreases in antioxidant enzymes in liver].

Rallidis LS, Paschos G, Papaioannou ML, et al. (2004). The effect of diet enriched with alpha-linolenic acid on soluble cellular adhesion molecules in dyslipidaemic patients. *Atherosclerosis*, 174, 127-132.[Flaxseed reduces the serum levels of sVCAM-1 but does not affect the levels of sICAM-1 and sE-selectin].

Ramaprasad TR, Baskaran V, Krishnakantha TP, et al. (2005). Modulation of antioxidant enzyme activities, platelet aggregation and serum prostaglandins in rats fed spray-dried milk containing n-3 fatty acid. *Mol Cell Biochem*, 280, 9-16.[n-3 fatty acids from flaxseed reduces platelet aggregation, and enhances the activity of hepatic antioxidant enzymes, catalase and glutathione transferase].

Ranhotra GS, Gelroth JA, Glaser BK, et al. (1993). Lipidemic responses in rats fed flaxseed oil and meal. *Cereal Chem*, 70, 364-366.[Flaxseed oil does not alter the serum levels of TG in rat].

Ratnayake WMN, Behrens WA, Fischer PWF et al. (1992). Chemical and nutritional studies of flaxseed (variety Linott) in rats. *J Nutr Biochem*, 3, 232-240.[Flaxseed in high dose reduces the serum levels of TG, TC and LDL-C].

Rhee Y, Brunt A. (2011). Flaxseed supplementation improved insulin resistance in obese glucose intolerant people: a randomized crossover design. *Nutr J*, 10, 44.[Flaxseed decreases insulin resistance which might be due to its antioxidant activity].

Rhee Y, Brunt A. (2009). Flaxseed lignan increased glucose uptake by human red cells. *The Open nutraceuticals* J, 2, 81-85.[Flaxseed lignin increases glucose uptake by red blood cells].

Rickard SE, Orcheson LJ, Seidl MM, et al. (1996). Dose-dependent production of mammalian lignans in rats and in vitro from the purified precursor secoisolariciresinol diglycoside in flaxseed. *J Nutr*, 126, 2012-2019.[Secoisolariciresinol diglucoside is metabolized to secoisolariciresinol, enterodiol, and enterolactone].

Rickard SE, Yuan YV, Thompson LU. (2000). Plasma insulin-like growth factor-1 levels in rats are reduced by dietary supplementation of flaxseed or its lignan secoisilariciresinol diglycoside. *Cancer Lett*, 161, 47-55.[Flaxseed and its lignan reduce the serum levels of insulin-like growth factor-1]

Ross R, Harker L. (1976). Hyperlipidemia and atherosclerosis. Science, 193, 1094-1100.[This study suggests that hyperlipidemia induces endothelial cell injury resulting in the development of atherosclerosis].

Ross R, Masuda J, Raines EW, et al. (1990). Localization of PDGF-B protein in macrophages in all phases of atherogenesis. *Science*, 248, 1009-1012.[PDGF- B protein is present in macrophages in atherosclerosis].

Saikku P. (1997). Chlamydia pneumoniae and atherosclerosis- an update. *Scand J Infect Dis Suppl*, 104, 53-56.[Chlamydia pneumonae is a risk factor of atherosclerosis].

Saikku P, Leinonen M, Mattila K et al. (1988). Serological evidence of an association of a novel Chlamydia, TWAR, with chronic coronary heart disease and acute myocardial infarction. *Lancet*, 8618, 983-986.[There is an association of chlamydia,TWAR with coronary heart disease and acute myocardial infarction].

Sanders TA, Roshanai F. (1983). The influence of different types of omega 3 polyunsaturated fatty acids on blood lipids and platelet function in healthy volunteers. *Clin Sci*, 64, 91-99.[Flaxseed does not alter serum levels of TC, LDL-C,HDL-C and TG in healthy subjects].

Schwab US, Callaway JC, Erkkilä AT, et al. (2006). Effects of hempseed and flaxseed oils on the profile of serum lipids, serum total and lipoprotein lipid concentrations and haemostatic factors. *Eur J Nutr*, 45, 470-477.[Flaxseed oil and hempseed oil have no effects on serum lipids except on TG which decreased significantly. Apo-B lipoprotein decreased].

Schwartz CJ, Valente AJ, Sprague EA. (1993). A modern view of atherogenesis. *Am J Cardiol*, 71, Suppl B:B9-B14.[This paper reports the modern view of development of atherosclerosis].

Shah PK, Falk E, Badimon JJ, et al. (1995). Human monocyte-derived macrophages induce collagen breakdown in fibrous caps of atherosclerotic plaques. Potential role of matrix-degrading metalloproteinases and implications for plaque rupture. *Circulation*, 92, 1565-1569.[This paper reports that human monocyte-derived macrophages induce collagen breakdown in fibrous caps of human atherosclerotic plaque associated with cellular expression of matrix metalloproteinase].

Sporn MB, Roberts AB, Wakefield LM, de Crombrugghe B. (1987). Some recent advances in the chemistry and biology of transforming growth factor-beta. *J Cell Biol*, 105, 1039-1043.[Transforming growth factor stimulates the synthesis of connective tissue and matrix including collagens ,proteoglycans and elastic fiber protein].

Statistics Canada, CAN SIM Table 102-0529: Deaths, by cause, Chapter IX: Diseases of the Circulatory System (100 to 199), age group and sex, Canada, annual (number), 2000 – 2006. Released May 4, 2010.[Statistics Canada reported that over one million Americans die from myocardial infarction each year].

Steinberg D. (1992). Antioxidants in the prevention of human atherosclerosis. *Circulation*, 85, 2337-2344.[This paper reports that antioxidants may prevent the development of atherosclerosis].

Stuglin C, Prasad K. (2005). Effect of flaxseed consumption on blood pressure, serum lipids, hemopoietic system and liver and kidney enzymes in healthy humans. *J Cardiovasc Pharmacol Therapeut*, 10, 23-27.[Flaxseed does not have deleterious effects on the hemopoietic system or renal and hepatic function and does not lower blood pressure and serum lipids in healthy humans].

Talom RT, Judd SA, McIntosh DD, McNeill JR. (1999). High flaxseed (linseed) diet restores endothelial function in the mesenteric arterial bed of spontaneously hypertensive rats. *Life Sci*, 64, 1415-1425.[Flaxseed has no effect on arterial pressure in both normotensive and hypertensive rats but restores endothelial cell function in mesenteric arterial bed of spontaneous hypertensive rats].

Tetta C, Bussolino F, Modena V, et al. (1990). Release of platelet-activating factor in systemic lupus erythematosus. *Int Arch Allergy Appl Immunol*, 91, 244-256.[platelet-activating factor is released in systemic lupus erythematosus].

The World Health Report. (2003). Shaping the future. www.WHO.int/whr/2003/en/whro3-en.pdf. [This report provides the data on worldwide cardiovascular death].

Thies F, Miles EA, Nebe-von-Caron G, et al. (2001). Influence of dietary supplementation with long-chain n-3 or n-6 polyunsaturated fatty acids on blood inflammatory cell populations and functions and on plasma soluble adhesion molecules in healthy adults. *Lipids*, 36, 1183-1193.[This paper reports the effects of dietary lon-chain n-3 or n-6 fatty acids on blood inflammatory cells and function , and soluble adhesion molecules].

Tou JC, Chen J, Thompson LU. (1998). Flaxseed and its lignan precursor, secoisolariciresinol dyglycoside, affect pregnancy outcome and reproductive development in rats. *J Nutr*, 128, 1861-1868.[Flaxseed had no effect on pregnancy outcome except lower birth weight and abnormal reproductive development in rats].

Wallace FA, Miles EA, Calder PC. (2003). Comparison of the effects of linseed oil and different doses of fish oil on mononuclear cell function in healthy human subjects. *Br J Nutr*, 89, 679-689.[This paper compares the effects of flaxseed oil and fish oil on mononuclear cells in human].

Westcott ND, Muir AD. Process for Extracting Lignans from Flaxseed. US Patent 5,705,618. (Jan. 6, 1998).[This patent describes the method of extracting lignans from flaxseed].

Westcott ND, Paton D. A complex containing lignan, phenolic and aliphatic substances from flax and process for preparing. US Patent 6,264,853 (July 24, 2001).[This patent describes the method for extracting flax lignan complex].

Wu H, Pan A, Yu Z, et al. (2010). Lifestyle counseling and supplementation with flaxseed or walnuts influence the management of metabolic syndrome. *J Nutr*, 140, 1937-1942.[This paper reports the influence of flaxseed or walnut in the management of metabolic syndrome].

Yamashita T, Oda E, Sano T, et al. (2005). Varying the ratio of dietary n-6/n-3 polyunsaturated fatty acid alters the tendency of thrombosis and progress of atherosclerosis in apoE-/- LDLR-/- double knockout mouse. *Thromb Res*, 116, 393-401.[This paper reports the effects of changing the ratio of n-6/n-3 on thrombosis and progression of atherosclerosis].

Yang L, Leung KY, Cao Y, et al. (2005). Alpha-linolenic acid but not conjugated linolenic acid is hypocholesterolaemic in hamsters. *Br J Nutr*, 93, 433-438.[Alpha-linolenic acid is hypocholesterolemic agent but conjugated linoleic acid is not].

Zhang W, Wang X, Liu Y, et al. (2008). Dietary flaxseed lignan extract lowers plasma cholesterol and glucose concentrations in hypercholesterolaemic subjects. *Br J Nutr*, 99, 1301-1309.[Flaxseed lignan extract is hypocholesterolemic and hypoglycemic agent].

Zhao G, Etherton TD, Martin KR, et al. (2004). Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. *J Nutr*, 134, 2991-2997.[Alpha-linolenic acid acts as hypolipidemic and anti-inflammatory agent].

Bibliography Sketches

Kailash Prasad received his B.Sc. (Distinction) in 1952 from Patna University, MBBS (Hons.) in 1957 from Bihar University, MD in 1961 from Delhi University, India, and Ph.D (Pharmacology) in 1967 from University of Alberta, Canada. He was a Lecturer in Lady Harding Medical College, University of Delhi, India from 1951 to 1964. He was Associate Professor in Pharmacology at the University of Alberta, Edmonton, then Associate Professor and full Professor in Physiology at the University of Saskatchewan Saskatoon, Canada. He was also an associate member and Adjunct Professor of Medicine at the University of Saskatchewan. Since 1997 he is Professor Emeritus in the Department of Physiology and Adjunct Professor of Medicine at the University of Saskatchewan. He is a fellow of the Royal College Physicians of Canada, American College of Cardiology, International Academy of Cardiovascular Sciences and International College of Angiology. He is a member and fellow of 18 medical and scientific societies. He has been and is a member of the editorial board of eight scientific journals and is a reviewer of manuscripts for 23+ scientific journals. He has held offices in the International College of Angiology as President, Member, Board of Directors and Chairman of the Scientific Committee. His research interest is in the role of oxygen radicals in cardiovascular diseases. He has published 205 refereed papers, 224 abstracts and 35 book chapters. He has 224 invited symposia/special presentations to his credit. He has co-edited *Textbook of Angiology* which has 1362 pages. He has been granted eight U.S. and Canadian

patents and one copyright. He has been involved in the development of PISA machine based on high frequency electrocardiogram for early detection, quantification and localization of ischemic heart disease. He has supervised 29 M.Sc./Ph.D. students. He has been an external examiner for 18 Ph.D. thesis of national and international universities. He has received 39 honors and awards including Lifetime Research Achievement Award for excellence in research from The Institute of Cardiovascular Sciences, St. Boniface General Hospital Research Centre, University of Manitoba, Centennial Medal from the Government of Saskatchewan for excellence in research and technology, Golden Wheel Award for excellence in science and technology from the Rotary Club of Saskatoon, Innovation Award for the creation of new technology for uses of flaxseed and its components from the University of Saskatchewan and Innovation Place and the John B. Chang Research Achievement Award for excellence in research and scholarly activity from the International College of Angiology. He taught medical students and received the Preclinical Teacher of the Year Award twice. He obtained FDA approval for "Beneflax" isolated from flaxseed for health benefits.