FLAXSEED IN CARDIOVASCULAR HEALTH AND DISEASE

Kailash Prasad
Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Keywords: antioxidant, atherosclerosis, cell adhesion molecules, chemokines, cytokines, flaxseed, flax lignan complex, flaxseed oil, inflammatory mediators, ischemic heart disease, monocyte colony stimulating factor, platelet aggregation, regression of atherosclerosis, secoisolariciresinol diglucoside, serum lipids, slowing of progression of atherosclerosis, stroke, suppression of atherosclerosis

Contents
1. Introduction
2. Flaxseed and its Components
3. Pharmacological Activity of Flaxseed and its Components
4. Mechanism of Atherosclerosis
5. Flaxseed and its Components on Mechanism of Atherosclerosis
6. Flaxseed and its Components on Risk Factors for Atherosclerosis
7. Flaxseed and its Components and Atherosclerosis
8. Health Benefits
9. Side Effects of Flaxseed and its Components
10. Conclusion
Glossary
Bibliography
Biographical Sketch

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 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 World 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 (Saikkku 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 glucoside is antioxidant.
6. Hydroxymethylglutaric acid (HMGA) is hypolipidemic agent.
7. Hypotensive.
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 artherosclerosis.

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 ipF2α isoprostane, a measure of lipid prooxidation 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 (O₂⁻), H₂O₂, ·OH and singlet oxygen (¹O₂), 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<sup>−/−</sup> 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).

Bibliography


Bassett CM, McCullough RS, Adel AL, Madding 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].


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].


This provides mechanism by which macrophage and foam cells can stimulate atherosclerosis.


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


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. However, increased the alpha-linolenic acid content of serum and mononuclear cells in blood].


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].


©Encyclopedia of Life Support Systems (EOLSS)
Flaxseed in Cardiovascular Health and Disease - Kailash Prasad

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].


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].


©Encyclopedia of Life Support Systems (EOLSS)

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. (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 lignin complex has no effect on serum electrolytes and enzymes related to liver function and biochemical parameters related to kidney function].


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, 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 atherosclerosis without affecting serum cholesterol. Suppression 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].


©Encyclopedia of Life Support Systems (EOLSS)


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].


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].


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].


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 long-chain n-3 or n-6 fatty acids on blood inflammatory cells and function, and soluble adhesion molecules.]


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.]


**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.