Flaxseed and Cardiovascular Health

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Abstract: Flaxseed and its components may improve cardiovascular health because of their numerous attributes. Flaxseed contains 35% of its mass as oil, of which 55% is α-linolenic acid (ALA). Flax meal, which is devoid of oil, contains the lignan secoisolariciresinol diglucoside (SDG). Flaxseed, flaxseed with very low ALA, flaxseed oil, flax lignan complex (FLC), and SDG reduce the development of hypercholesterolemic atherosclerosis by 46%, 69%, 0%, 73%, and 34%, respectively, in the rabbit model. FLC and SDG slow the progression of atherosclerosis but have no effect in regression of atherosclerosis. Suppression of atherosclerosis by flaxseed is the result of its lignan content and not the result of ALA content. Suppression of atherosclerosis is associated with lowering of serum lipids and antioxidant activity. Effects of flaxseed on serum lipids in experimental animals are variable from no change to slight reduction. Flaxseed oil does not affect serum lipids, except for a slight reduction in serum triglycerides. Lignan in general reduces serum total cholesterol and low-density lipoprotein cholesterol and raises serum high-density lipoprotein cholesterol. SDG and its metabolites have antioxidant activity. Flaxseed and flaxseed oil do not have antioxidant activity except they suppress oxygen radical production by white blood cells. Flaxseed oil/ALA has variable effects on inflammatory mediators/markers (interleukin [IL]-1β, IL-2, IL-4, IL-6, IL-10, tumor necrosis factor-α, interferon-gamma, C-reactive protein, and serum amyloid A). Doses of ALA less than 14 g/d do not affect inflammatory mediators/markers, but 14 g/d or greater reduce inflammatory mediators/markers. Flaxseed oil decreases soluble vascular cell adhesion molecule-1 but has no effect on soluble intracellular adhesion molecule-1, soluble E-selectin, and monocyte colony-stimulating factor. Flaxseed has variable effects on IL-6, high-sensitivity C-reactive protein, and soluble vascular cell adhesion molecule-1. FLC reduces plasma levels of C-reactive protein but has no effects on IL-6, tumor necrosis factor-α, soluble intracellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, or monocyte chemoattractant protein. Flaxseed has a very small hypotensive effect, but flaxseed oil does not lower blood pressure. However, SDG is a very potent hypotensive agent. Flaxseed oil decreases platelet aggregation and increases platelet activating inhibitor-1 and bleeding time. Flaxseed and FLC have no effect on the hemopoietic system. SDG is a potent angiogenic and antiapoptotic agent that may have a role in cardioprotection in ischemic heart disease. In conclusion, flaxseed, FLC, and SDG, but not flaxseed oil, suppress atherosclerosis, and FLC and SDG slow progression of atherosclerosis but have no effect on regression. Flaxseed oil suppresses oxygen radical production by white blood cells, prolongs bleeding time, and in higher doses suppresses serum levels of inflammatory mediators and does not lower serum lipids.

Key Words: flaxseed, flaxseed oil, lignan, atherosclerosis, oxidative stress, inflammatory mediators

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death, accounting for 35.2% of all deaths in 2005.[1] Coronary artery disease (CAD) caused 20% of all deaths.[1] Atherosclerosis and its complications such as CAD and CVD remain major causes of mortality and morbidity in the Western world. Major risk factors of atherosclerosis include hypercholesterolemia, hypertension, diabetes, smoking, obesity, and inflammation. The prevalence of high levels of low-density lipoprotein cholesterol (LDL-C) in US adults was 25.3% in 1999 to 2004.[1] An estimated 80.7 million (one in three) American adults have one or more types of CVD.[1] Prevalence of hypertension and CAD in the American population is 73 million and 16 million, respectively. Every 1% increase in serum cholesterol increases the risk of 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.[2] Numerous strategies have been developed to reduce risk factors such as hypercholesterolemia, hypertension, inflammatory mediators, and oxidative stress in an attempt to reduce the development of atherosclerosis and hence a reduction in CAD.

This review article deals with the effectiveness of flaxseed and its components, lignan and flaxseed oil, in the prevention, slowing of progression, and regression of hypercholesterolemic atherosclerosis and in the lowering of serum lipids, inflammatory mediators, oxidative stress, and blood pressure in experimental animals and in humans.

FLAXSEED AND ITS COMPONENTS

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.[3,4] It is the richest source of a lignan called secoisolariciresinol diglucoside (SDG).[5] Flax meal, which is

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devoid of oil, is approximately 55% to 68% of the flaxseed mass and contains approximately 16.4 mg/g of SDG. The level of SDG in flaxseed varies between 0.6 and 1.8 g/100 g.[6] Flax lignan complex (FLC), isolated from flaxseed, contains 34% to 38% SDG, 15% to 21% cinnamic acid glucoside, and 9.6% to 11.0% hydroxymethylglutaric acid by weight.[7] SDG is metabolized to secoisolariciresinol (SECO), enterodiol (ED), and enterolactone (EL) in the body.[8] SDG,[9,10] SECO, ED and EL,[10] and cinnamic acid[11] are antioxidants. Hydroxymethylglutaric acid is a hypolipidemic agent.[12]

FLAXSEED

Atherosclerosis, Serum Lipids, Inflammatory Mediators, and Oxidative Stress

Animal Studies

Oxygen radicals (ORs) have been implicated in the pathogenesis of hypercholesterolemic atherosclerosis.[13–15] Dietary n-3 fatty acid supplementation reduces the production of inflammatory mediators and leukotriene B_4,[16] suppresses bursts of polymorphonuclear leukocytes (PMNLs),[17] and reduces production of superoxide anion (O_2^-) and chemiluminescence (CL) (oxygen radical release) in monocytes.[18] The effects of flaxseed (7.5 g/kg body weight/d) on high cholesterol diet (1% cholesterol)-induced atherosclerosis, serum lipids, and OR-producing activity of PMNLs in rabbits were investigated by Prasad.[19] He reported that a high cholesterol diet increased the serum total cholesterol (TC) and OR-producing activity of PMNLs (PMNL-CL) without any effect on serum triglycerides (TG) and produced atherosclerosis. Flaxseed suppressed the development of atherosclerosis by 46%, and this was associated with suppression of PMNL-CL in the hypercholesterolemic rabbit. Flaxseed increased the serum TC without affecting the serum TG. Flaxseed increased the levels of serum TC and decreased PMNL-CL in normocholesterolemic rabbits. These data suggest that flaxseed reduces hypercholesterolemic atherosclerosis without affecting serum lipids and that its antiatherogenic effect may be the result of suppression of OR production by PMNLs by ALA or the antioxidant activity of SDG.

Ratnayake et al[20] reported that in the rat, a 10% flaxseed diet did not affect serum lipids, but 20% and 30% flaxseed diets reduced plasma TC, LDL-C, and TG by 21% and 33%, 33.7% and 67%, and 23% and 23%, respectively. Flaxseed diet reduced serum TC and LDL-C without affecting serum TG in rats.[21] Suppression of hypercholesterolemic atherosclerosis by a 10% flaxseed diet in rabbits was associated with a decrease in serum TG without any effect on serum TC.[22] Flaxseed, however, did not alter the levels of serum TG and TC in normocholesterolemic rabbits. In another study, Dupasquier et al[23] reported a dose-dependent suppression of hypercholesterolemic atherosclerosis by flaxseed in LDL receptor-deficient ($LDLR^{-/-}$) mice and this effect was associated with a decrease in serum TC without an effect on serum TG. These authors reported an increased expression of interleukin-6 (IL-6) and vascular cell adhesion molecule-1 (VCAM-1) in the aortic tissue of hypercholesterolemic $LDLR^{-/-}$ mice. They also reported that flaxseed diet reduced the expression of IL-6 and VCAM-1 in the aortic tissue of hypercholesterolemic mice. It was noted that flaxseed did not alter the levels of serum TC and expression of IL-6 and VCAM-1 in normocholesterolemic mice.

Consumption of flaxseed (7.5%, 15%, or 22% in the diet) in overiectomized Golden Syrian hamsters reduced atherosclerosis in a dose-dependent manner.[24] It also reduced serum cholesterol levels. There was no effect on non-high-density lipoprotein (HDL) or esterified cholesterol, but the levels of serum TG increased with the flaxseed diet in this study. Regular diet supplemented with flaxseed (15%) in streptozotocin-induced diabetic Golden Syrian hamsters produced significant reductions in serum TC (24.9%) and TC/HDL-C ratio (60%) and an increase in serum HDL-C (91%).[25]

Human Studies

In hyperlipidemic individuals, consumption of 15 g/d flaxseed for 3 months was associated with a reduction of serum TC and LDL-C by 18 mg/dL and 19 mg/dL, respectively.[26] The levels of serum HDL-C remained unaltered in this study. In two other studies,[27,28] consumption of similar doses of flaxseed (50 g/d) for a similar duration (4 weeks) in healthy individuals had different effects on serum lipids. Flaxseed consumption of 50 g/d for 4 weeks reduced serum TC and LDL-C by 9% and 18%, respectively.[27] Consumption of flaxseed (50 g/d) for 4 weeks in the second study resulted in reductions of plasma TC and LDL-C by 6% and 9%, respectively.[28] Flaxseed consumption of 30 g/d for 4 weeks reduced serum TC and LDL-C by 11% and 12%, respectively.[29] They also reported that with higher doses of flaxseed, the reductions in TC and LDL-C were lower than with smaller doses. Consumption of flaxseed (20 g/d) for 2 months in hyperlipidemic individuals resulted in reductions of serum TC (17.2%), LDL-C (3.9%), TG (36.3%), and TC/HDL-C ratio (33.5%).[30] Daily consumption of flaxseed (32.7 g) for 4 weeks did not alter the serum levels of TC, LDL-C, HDL-C, and very low-density lipoprotein cholesterol (VLDL-C) in 15 healthy men between 22 and 47 years of age, but increased the serum levels of TG.[31] The serum levels of total bilirubin, aspartate aminotransferase, alkaline phosphatase, protein, albumin, glucose, and urea remained unaltered, but serum levels of creatinine decreased in this study. Levels of hemoglobin and counts of red blood cells, white blood cells (WBC), and neutrophils remained unaltered with flaxseed diet in this study.

The results of a double-blind, randomized, controlled clinical trial in men and postmenopausal women with flaxseed (40 g/d) for 10 weeks showed that flaxseed reduced LDL-C by 13% at 5 weeks and 7% at 10 weeks.[32] In this study, there was a reduction of lipoprotein a by 14% at 10 weeks. Inflammatory markers (IL-6 and high-sensitivity C-reactive protein [hs-CRP]) were not affected. Flaxseed reduced HDL-C by 16% and 9% at 5 and 10 weeks, respectively. A randomized, double-blind, placebo-controlled trial in healthy menopausal women showed that 40 g/d flaxseed for 12 months increased apolipoproteins A-1 and B (by 4.4% and 3%) and lipoprotein a and decreased LDL peak particle size.[33] In 55 mild to moderately hypercholesterolemic Native American postmenopausal women, flaxseed (30 g/d) for 3 months reduced serum TC (7%) and LDL-C (10%).[34] The levels of serum HDL-C,

TG, and hematologic parameters remained unaltered in this study.

These results suggest that flaxseed consistently suppresses the development of atherosclerosis in experimental animal models. However, its effect on serum lipids is variable. The results in humans show that flaxseed (15–50 g/d) reduces TC and LDL-C by 1.6% to 18% in both normocholesterolemic and hypercholesterolemic individuals without significant effects on HDL-C and TG. The results are not consistent and in some studies, it has been reported that flaxseed has no effect on LDL-C in hypercholesterolemic healthy individuals.

FLAXSEED WITH VERY LOW α-LINOLENIC ACID

Atherosclerosis, Serum Lipids, and Oxidative Stress

The antiatherogenic effects of flaxseed may be the result of ALA, lignans, or both. ALA in fish oil has been reported to suppress hypercholesterolemic atherosclerosis.[35] If the antiatherogenic effect of flaxseed is the result of its ALA content, then flaxseed without ALA would have no antiatherogenic activity. Prasad et al[6] used CDC-flaxseed, which has similar oil content (35% of total mass), and SDG (15.4 versus 16.4 mg/g defatted meal) as ordinary flaxseed, but only 2% to 3% ALA content. CDC-flaxseed in the dose of 7.5 g/kg per day for 8 weeks reduced the serum levels of TC (14%), LDL-C (17%), and TC/HDL-C ratio (28%); increased serum TG and VLDL-C; and had no effect on HDL-C in hypercholesterolemic rabbits. This variety of flaxseed suppressed the development of atherosclerosis by 69%. It had no effect on the serum lipid levels in normocholesterolemic rabbits. The results suggest that the antiatherogenic effect of flaxseed is not the result of ALA and may be attributable to the lignan content of flaxseed. No human study has been reported with CDC-flaxseed.

FLAXSEED OIL

Atherosclerosis and Serum Lipids

Flaxseed oil was used to determine if ALA is involved in the antiatherogenic effect of flaxseed.[36] The authors reported that flaxseed oil (5% in diet, equivalent to 7.5 g flaxseed/kg per day) did not prevent the development of hypercholesterolemic (0.5% cholesterol diet) atherosclerosis and also did not affect the levels of serum TC, LDL-C, HDL-C, TG, and the ratio of TC/HDL-C. Flaxseed oil also did not affect the serum lipids in normocholesterolemic rabbits. In one study, it has been reported that the extent of atherosclerosis was less in apoE$^{-/-}$ LDLR$^{-/-}$ double knockout mice fed with a low n-6/n-3 fatty acid ratio compared with the high n-6/n-3 ratio group.[37] The lowest n-6/n-3 ratio was the most effective in suppressing atherosclerosis.

ALA (20 g/kg diet) isolated from flaxseed fed to Golden Syrian hamsters for 6 weeks reduced serum cholesterol by 17% to 21%.[38] Flaxseed oil did not reduce serum TG in hypercholesterolemic rats.[39] The data on the effects of flaxseed oil on serum lipids are much less consistent with studies showing a modest reduction in TG with large doses (60 mL/d), but most reports show no effect in humans.[40] Consumption of flaxseed oil (15 mL/d) for 12 weeks produced a small decrease in HDL-C (from 1.12 to 1.08 mmol/L) and apo A-1 levels (from 1.28 to 1.24 g/L) in ε3/ε3 homozygous dyslipidemic patients.[41] Flaxseed oil decreased plasma TG (23%), TC (12%), and HDL-C (10%) in men expressing an atherogenic lipoprotein phenotype.[42] Other investigators[43,44] have reported no changes in serum TC, LDL-C, and HDL-C in hyperlipidemic patients. No changes in serum TC, TG, LDL-C, and HDL-C with flaxseed oil have also been reported in healthy subjects.[45,46] Paschos et al[47] reported a slight decrease of 4.3% in serum HDL-C and no change in the serum TG, TC, and LDL-C with flaxseed oil. No effect was observed on the serum total lipoprotein cholesterol concentration, except there was a reduction in serum TG and apo-B in healthy volunteers.[48] Kelley et al[49] reported that flaxseed oil for 56 days did not significantly alter the serum levels of TG, TC, HDL-C, or LDL-C.

Flaxseed Oil and Inflammatory Mediators

Inflammatory mediators are involved in numerous cardiovascular diseases, including atherosclerosis and rheumatoid arthritis. Atherogenesis is mediated by local or systemic production of inflammatory cytokines, and several inflammatory markers have been related to increased risk for CVD, including CRP, serum amyloid A (SAA), IL-6, and tumor necrosis factor-α. (TNF-α).[50,51] There has been much interest in the effects of ALA on inflammatory mediators/markers. Flaxseed oil/ALA has variable effects on these mediators depending on the doses of ALA.

ALA intake of 9.5 g/d (equivalent to 17 mL of flax oil) does not alter the functional activity of neutrophils, monocytes, and lymphocytes in humans.[52] A moderate amount of ALA (2 g/d) for 12 weeks did not affect production of TNF-α, IL-1β, IL-6, or soluble intracellular adhesion molecule-1 (sICAM-1), but decreased sVCAM-1 and sE-selectin.[53] ALA and fish oil had similar effects and did not affect inflammatory cell numbers, phagocytosis, or respiratory burst in this study. Consumption of 3.5 g/d ALA for 12 weeks in healthy individuals did not affect production of TNF-α, IL-1β, IL-2, IL-4, IL-10, or interferon-γ.[54] In humans, ALA (2 g/d) did not affect IL-2 or interferon-γ.[53] However, doses of ALA at 12 g/d or greater depressed the levels of cytokines. ALA (14 g/d for 4 weeks) significantly decreased TNF-α and IL-1β production by mononuclear cells in humans.[55] Flaxseed oil (15 mL/d for 12 weeks) decreased IL-6 in healthy humans.[41] Six percent ALA in the diet decreased IL-6 and IL-10, and increased TNF-α in mice.[56]

Flaxseed oil affects inflammatory markers as well. In a well-controlled trial in healthy abdominally obese adult males and females, flaxseed oil treatment for 8 weeks did not change CRP, SAA, IL-6, and TNF-α.[57] However; Zhao et al[58] showed that flaxseed oil lowered CRP after 6 weeks of administration.

It has been reported that flaxseed oil lowers CRP, SAA, and IL-6 in dyslipidemic males.[59,60] ALA at a dose of 8.1 g/d decreases SAA, CRP, and IL-6.[61] Lowering of CRP and SAA with 15 mL of flaxseed oil consumed daily for 12 weeks has also been reported in humans.[41]

Flaxseed Oil/α-Linolenic Acid and Adhesion Molecules

Flaxseed oil alters cell adhesion molecules. Flaxseed oil (15 mL/d) for 12 weeks decreased sVCAM-1 but had no effect on sICAM-1 and sE-selectin in dyslipidemic patients.[62] ALA (2 g/d) consumption for 12 weeks decreased sVCAM-1 and sE-selectin by 16% and 23%, respectively, but had no effect on sICAM-1, which is the result of monocyte activation.[53] sVCAM-1 and E-selectin are almost exclusively expressed by endothelial cells.[63] Flaxseed oil (15 mL/d for 12 weeks) decreased the serum levels of monocyte colony-stimulating factor.[41]

Flaxseed Oil and Hemostatic Factors

A study in rabbits has shown that flaxseed oil inhibited platelet aggregation induced by both thrombin and fibrinogen but not induced by adenosine.[64] The n-6/n-3 ratio (0.29:8) using flaxseed oil and safflower oil had a dose-dependent antithrombotic effect in apoE$^{-/-}$ LDLR$^{-/-}$ double knockout mice.[37] The lowest n-6/n-3 ratio was the most effective in suppressing thrombosis. ALA (5.9 g/d for 12 weeks) increased bleeding time and platelet activating inhibitor-1, decreased platelet aggregation and thromboxane B_2 production, and had no effect on fibrinogen or factor VIIc.[45]

In a small study in healthy men, flaxseed oil in the dose of 40 g/d for 23 days[65] and 5.9 g/d[66] reduced platelet aggregation. However, a larger study found no antiplatelet activity with low or high doses of flaxseed oil.[67] No significant changes in coagulation factors (factor II, factor V, factors VII-X, and fibrinogen) in the plasma of rats fed flaxseed oil have been reported.[68] ALA has been associated with increased bleeding time.[69]

Flaxseed Oil and Blood Pressure

A study on the relationship between adipose tissue fatty acids and blood pressure in healthy male subjects was made by Berry and Hirsch.[70] They reported that an absolute 1% increase in adipose tissue ALA was associated with a decrease of 5 mmHg in systolic, diastolic, and mean arterial pressures. Flaxseed oil (9.2 g ALA/d for 6 weeks) did not affect arterial pressure, whereas fish oil (3.4 g/d of eicosapentaenoic acid and docosahexaenoic acid) reduced systolic arterial pressure by 5 mmHg.[71] Similarly, Nestel et al[72] reported that flaxseed oil (20 g/d ALA) had no effect on arterial pressure.

Flaxseed Oil and Antioxidant Activity

Lipid peroxidation was elevated in heart, liver, and aortic tissues in rats treated with flaxseed oil, and this effect was associated with reduced superoxide dismutase.[73] Flaxseed oil did not affect the activity of catalase and superoxide dismutase in livers of monkeys in vivo and in vitro.[74] n-3 Fatty acids from flaxseed oil increased the activity of the antioxidant enzymes catalase and glutathione peroxidase in rats.[75] Flaxseed oil (5% in the diet) given for 2 months had no effect on serum or aortic malondialdehyde (MDA) and antioxidant reserve of the aorta, but decreased the OR-producing activity of WBC in hypercholesterolemic rabbits.[36] However, aortic MDA was elevated and aortic antioxidant reserve was low with flaxseed oil in rabbits on a regular diet.[36]

SECOISOLARICIRESINOL DIGLUCOSIDE

The data on flaxseed,[19] flaxseed with very low ALA,[6] and flaxseed oil[36] suggested that the antiatherogenic activity of flaxseed is not the result of ALA but may reside in the flax meal, which contains SDG, cinnamic acid glucoside, and hydroxymethylglutaric acid.[7]

Secoisolariciresinol Diglucoside and Suppression of Atherosclerosis

Prasad[13] investigated the effects of SDG on serum lipids, oxidative stress, and development of atherosclerosis in hypercholesterolemic and normocholesterolemic rabbits. SDG (15 mg/kg body wt/d) for 8 weeks reduced the serum levels of TC by 33%, LDL-C by 35%, and ratio of TC/HDL-C by 64% in hypercholesterolemic (1% cholesterol diet) rabbits. SDG initially (at 4 weeks) raised the serum level of HDL-C by greater than 140%, but it remained unchanged at 8 weeks in hypercholesterolemic rabbits. Serum levels of TG remained unchanged, but VLDL-C levels decreased with SDG in hypercholesterolemic rabbits. The levels of aortic MDA were lower and antioxidant reserve (aortic-CL) was higher in hypercholesterolemic rabbits with SDG compared with hypercholesterolemic rabbits without SDG. SDG had no effect on serum levels of TC, LDL-C, HDL-C, aortic MDA, and aortic-CL, but decreased the serum levels of TG and VLDL-C in normocholesterolemic rabbits. SDG suppressed the development of hypercholesterolemic atherosclerosis by 73% in this study. Prasad[13] also reported that hypercholesterolemia is associated with increased oxidative stress in the aorta, ie, an increase in aortic MDA and decrease in antioxidant reserve. These results suggest that the antiatherogenic effect of SDG may be the result of the reduction in serum lipids, and its antioxidant activity.

SDG (1% in the diet) reduced the serum levels of TG (38%) and TC (15%) in high fat-fed mice.[76] SDG (20 mg/kg body wt/d for 8 weeks) reduced serum levels of TC, TG, and LDL-C by 33%, 39%, and 45%, respectively, and raised HDL-C levels by 22% in hypercholesterolemic rats.[77]

Secoisolariciresinol Diglucoside and Regression of Atherosclerosis

The effect of SDG (20 mg/kg body wt/d) on regression of hypercholesterolemic atherosclerosis in rabbits was investigated by Prasad.[78] He observed that a regular diet (2 months) after a high cholesterol diet (2 months) accelerated atherosclerosis by 49% and this progression was prevented by SDG treatment for 2 or 4 months. Prevention of progression of atherosclerosis was associated with reduction in oxidative stress in the aorta. SDG treatment for 2 months did not regress, but for 4 months did produce regression of atherosclerosis by 17.5% (not significant).

Antioxidant Activity of Secoisolariciresinol Diglucoside and Its Metabolites

Using high-pressure liquid chromatography, Prasad[9] has shown that SDG scavenges hydroxyl radical (·OH) generated by photolysis of hydrogen peroxide (H_2O_2) with ultraviolet light and trapped with salicylic acid, and this effect was concentration-dependent. He also reported that SDG prevented

·OH-induced lipid peroxidation of liver homogenate in a concentration-dependent manner.[9] Prasad[10] measured the antioxidant activity of SDG and its metabolites SECO, EL, and ED using the ability of these compounds to reduce the PMNL-CL. The activated PMNLs generate O^{-}_{2}, H_2O_2, ·OH, and singlet oxygen ($^1O_2$). SDG, SECO, EL, and ED produced concentration-dependent reductions in PMNL-CL, suggesting that they have antioxidant activity. The antioxidant potencies of SDG, SECO, EL, and ED were 1.27, 4.86, 4.35, and 5.02, respectively, as compared with vitamin E. SECO, EL, and ED are 3.82, 3.95, and 3.43 times more potent, respectively, than SDG as antioxidants.

Secoisolariciresinol Diglucoside and Blood Pressure

Prasad[79] investigated the effects of various doses of SDG (3, 5, 10, 15, and 20 mg/kg intravenously) on arterial pressures in anesthetized rats. SDG in the doses of 3, 5, and 10 mg/kg produced dose-dependent reductions in systolic, diastolic, and mean arterial pressures. Doses of 15 and 20 mg/kg of SDG had effects similar as the 10-mg/kg dose. The maximum effect was at 15 to 20 minutes after SDG administration. The arterial pressures tended to recover after 15 to 20 minutes, but even at the end of 4 hours, the percent reductions in mean arterial pressures were 11, 21, 33, 22, and 29, respectively, with 3, 5, 10, 15, and 20 mg SDG. Pretreatment with N^G-monomethyl-L-arginine, an inhibitor of nitric oxide synthase, did not prevent the SDG-induced reduction in arterial pressure. Pretreatment with methylene blue, a nonspecific, and oxadiazolo quinoxalin, a specific inhibitor of guanylate cyclase, completely prevented the SDG-induced reduction in arterial pressure. These results suggest that SDG is a long-acting hypotensive agent and that the hypotensive effect is mediated through the guanylate cyclase enzyme.

Secoisolariciresinol Diglucoside and Ischemia–Reperfusion Myocardial Injury

Penumathsa et al[80] have shown in an ex vivo ischemia/reperfusion model of hearts of rats pretreated with SDG (20 mg/kg body wt/d for 2 weeks orally) that SDG reduced the myocardial infarct size by 32% and also decreased cardiomyocyte apoptosis. SDG increased protein expression of vascular endothelial growth factor (VEGF), angiopoietin-1, and phosphorylated endothelial nitric oxide synthase (p-eNOS). SDG increased capillary density and myocardial function in this model. They also reported that SDG increased tubular morphogenesis in human coronary arteriolar endothelial cells. SDG increased the expression of VEGF, angiopoietin-1, and p-eNOS in human coronary arteriolar endothelial cells. The results suggest that SDG is a potent angiogenic and antiapoptotic agent and may have a role in cardioprotection in ischemic heart disease.

In a study on hypercholesterolemic rats, Penumathsa et al[77] showed that pretreatment with SDG (20 mg/kg body wt/d for 2 weeks) reduced the ischemia-reperfused myocardial infarct size by 20% and improved left ventricular function. SDG-treated rats showed increased capillary density (2531 versus 1901) and arteriolar density (2.6 versus 1.8). These changes with SDG were shown to be associated with increased expression of VEGF, p-eNOS, and heme oxygenase-1. The results suggest that increased expression of VEGF, p-eNOS, and heme oxygenase-1 with SDG might have resulted in improved cardiac function resulting from increased neovascularization of ischemic hypercholesterolemic myocardium.

FLAX LIGNAN COMPLEX

Flax Lignan Complex and Suppression of Atherosclerosis

Flax lignan complex in the dose of 40 mg/kg body wt/d in the diet for 8 weeks in rabbits suppressed the development of hypercholesterolemic atherosclerosis by 34.37%, and this was associated with decreases in serum TC by 20%, LDL-C by 14%, TC/HDL-C ratio by 34%, serum MDA by 35%, and aortic MDA by 58% and elevation of HDL-C by 30%.[81] Prasad also reported that FLC had no effect on serum TG but decreased antioxidant reserve. In normocholesterolemic rabbits, FLC had no effect on serum TG, TC, LDL-C, and MDA, but it increased the levels of HDL-C by 25% and aortic MDA by 133%. FLC in doses providing 300 or 600 mg (in two divided doses daily) for 8 weeks were given to 18 male and 20 female hypercholesterolemic individuals.[82] The 300-mg dose of FLC reduced TC by 15.47% and LDL-C by 17.04%. The 600-mg dose of FLC reduced the serum levels of TC by 24.2% and LDL-C by 22.0%. HDL-C levels were slightly decreased with FLC (600 mg). The ratio of TC/HDL-C decreased with the 600-mg dose but not with the 300-mg dose. However, the data of Hallund et al[83] on serum lipids were opposite to that described. They reported that FLC, in a dose providing 500 mg SDG/d for 6 weeks in a randomized, double-blind, placebo-controlled crossover study in healthy postmenopausal women, had no effect on serum TC, TG, LDL-C, or HDL-C. These differences could be the result of the difference in the lipid status of the study subjects. Antioxidant capacity measured by Trolox-equivalent antioxidant capacity and ferric-reducing ability of plasma was not affected by FLC.[83]

Flax Lignan Complex and Slowing of Progression of Atherosclerosis

Prasad[84] investigated the efficacy of FLC in slowing the progression of already developed hypercholesterolemic atherosclerosis. FLC was effective in slowing the progression of atherosclerosis by 31%. This effect was associated with a decrease in the aortic MDA by 42% and aortic-CL (antioxidant reserve) by 43%. It is to note that an increase in aortic-CL indicates a decrease in the antioxidant reserve and vice versa. Slowing of progression of atherosclerosis was not associated with any change in OR-producing activity of WBC or serum lipids.

Flax Lignan Complex and Regression of Atherosclerosis

A study was conducted by Prasad[85] to investigate if FLC was effective in regression of already developed hypercholesterolemic atherosclerosis in rabbits. He reported that FLC, although effective in preventing the acceleration of atherosclerosis by 32%, after replacement of a high cholesterol diet with a regular diet, was not effective in regression of already

developed atherosclerosis. The ineffectiveness of FLC in regression of atherosclerosis was associated with no changes in aortic-CL, aortic MDA, WBC-CL, or serum MDA. However, prevention of acceleration of atherosclerosis with FLC was associated with a reduction in aortic MDA. The results suggest that FLC did not regress already developed atherosclerosis in this study. A study using higher doses for a prolonged period should be conducted to see if FLC regresses atherosclerosis.

Flax Lignan Complex and the Hemopoietic System

The effects of FLC (40 mg/kg body wt/d orally for 2 months) on the hemopoietic system were investigated in normo- and hypercholesterolemic rabbits by Prasad.[86] FLC had no adverse effects on counts of red blood cells, WBC, granulocytes, lymphocytes, monocytes, and platelets in both normo- and hypercholesterolemic rabbits. The values for mean corpuscular volume, red cell distribution width, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and platelet volume remained unaltered in both normo- and hypercholesterolemic rabbits with FLC treatment. Results suggested that short-term use of FLC does not have adverse effects on the hemopoietic system.

Flax Lignan Complex and Serum Enzymes and Electrolytes

Short-term use of FLC does not affect serum electrolytes (sodium, potassium, chloride, and bicarbonate), serum enzymes (aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, and gamma-glutamyl transferase), serum albumin, or creatinine in rabbits on a regular diet for 4 months after a high cholesterol diet for 2 months.[87]

Flax Lignan Complex and Inflammatory Markers

The effects of FLC in a dose providing 500 mg SDG/d for 6 weeks on CRP, IL-6, TNF-α, sICAM-1, sVCAM-1, and monocyte chemoattractant protein-1 in 22 healthy postmenopausal women were investigated by Hallund et al.[88] FLC significantly reduced the plasma concentration of CRP but had no effect on IL-6, TNF-α, sICAM-1, sVCAM-1, or monocyte chemoattractant protein-1.

Potential Mechanisms of Health Benefits of Flaxseed and Its Components

The potential mechanisms of the health benefits of flaxseed and its components are summarized in Table 1. Flaxseed and its components may have health benefits because of the attributes shown in Table 1. It is to be noted that not all attributes are present in all components. The studies to date suggest that most health benefits are available in the use of SDG and FLC.

Potential Concerns in the Use of Flaxseed and Flaxseed Oil

Flaxseed and its components may have protective effects against cardiovascular disease through numerous mechanisms,

TABLE 1. Potential Mechanisms of Health Benefits of Flaxseed and Its Components

	Flaxseed	Flaxseed Without ALA (2–3%)	Flaxseed Oil	SDG	FLC
Atherosclerosis Suppression	46% [19]	69% [6]	0% [36]	73% [13]	34% [81]
Slowing of progression	—	—	—	Yes (24–44%) [78]	Yes (31%) [84]
Regression	—	—	—	Yes (18%) [78]	No [85]
Lipids TC	Variable effects (small) ↓, ↔ [19,20,23,26–32]	↓ [6]	↔ [36,45,46,49]	↓↓ [13,76,77]	↓ [81,82]
LDL-C	Variable effects ↓, ↔ [19,20,23, 26–32]	↓ [6]	↔ [36,45,46,49]	↓↓[13,77]	↓ [81,82]
HDL-C	↔ [19,20,23,26–32]	↔ [6]	↔ [36,45,46,49]	↑ [13,77]	↑ [81,82]
TG	Variable effects ↓, ↔ [19,20,23,26–32]	↑ [6]	↔ [36,45,46,49]	↓, ↔ [13,76,77]	↔ [81]
Antioxidant activity	Only ↓ WBC–CL [19]	Yes [6]	Only ↓ WBC–CL [36]	↓↓ [9,10]	↓ [81]
Anti-inflammatory activity	—	—	Yes (in large doses) [41,55,56,59,60]	—	Yes [88]
Anticoagulant activity	—	—	Yes [37,45,64,65,69]	—	—
Angiogenic activity	—	—	—	Yes [77,80]	—
Antiapoptotic activity	—	—	—	Yes [80]	—
Expression of VEGF	—	—	—	↑ [77,80]	—
Expression of heme oxygenase	—	—	—	↑ [77]	—
Hypotensive activity	—	—	—	Yes (marked) [79]	—
Protection against I/R injury	—	—	—	Yes [80]	—

Most of the statements in this table are "yes" or "no" because of the variations in the data. The numbers in square brackets are the reference numbers. SDG, secoisolariciresinol diglucoside; FLC, flax lignan complex; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; ALA, alpha linolenic acid; VEGF, vascular endothelial growth factor; WBC-CL, white blood cell chemiluminescence (oxygen radical production by WBC); I/R, ischemia/reperfusion; ↑, increase; ↓, decrease; ↓↓, marked decrease; –, no study done; ↔, no change.

including reductions in serum TC, LDL-C, inflammatory markers, platelet aggregation and expression of adhesion molecules, and their antioxidant activity. It is of note, however, that the most active ingredient of flax seed is lignan. Antiatherosclerotic activity is mainly the result of the lignan component of flaxseed and not its oil content. A common question asked by consumers of flaxseed is if flaxseed or flaxseed oil is safe to use. Besides lignans, flaxseed contains phytic acid, cyanogenic glycosides, and cadmium.

The phytic acid content of flaxseed is approximately 0.80% to 1.5% of the dry seed.[89] It has dual roles. It inhibits absorption of calcium and iron but reduces colon cancer in animal models.

The cyanogenic glycoside content of flaxseed is 0.1% of the dry weight, whereas its content in young green seed is 5%.[90] It is believed that an adult can detoxify from 30 to 100 mg of cyanide per day. An adult can consume more than 1 kg of ground flaxseed daily before exhibiting cyanide toxicity. The amount of flaxseed consumed in cereals, muffins, or flax bread does not pose problems with regard to cyanogenic glycosides. Cyanide is not detected after cooking. Use of greater than 10 tablespoons/d uncooked flax meal may raise cyanogenic glycoside levels above 50 to 60 mg of inorganic cyanide, which is considered potentially toxic in adults.[91] However, 50 g/d of baked flaxseed powder does not increase urinary thiocyanate levels.[27] There are no data on the safety of flaxseed in pregnancy and lactation or in children. In rats, however, 10% flaxseed in the diet produced lower birth weights and hormonal effects in both males and females.[92]

Flaxseed also contains a small amount of cadmium in the range of 0.2 to 0.6 mg/kg.[93] The risk to health from the amount of cadmium in flaxseed is considered considerably lower than the risk from consumption of rice or wheat.[90]

Flaxseed oil does not lower serum lipids and does not prevent the development of atherosclerosis. Flaxseed oil in moderate doses does not affect inflammatory mediators. However, in larger doses, it suppresses the production of inflammatory mediators. Flaxseed oil consumption increases eicosapentaenoic acid but does not increase docosahexaenoic acid, whereas fish oil increases both eicosapentaenoic acid and docosahexaenoic acid. For flaxseed oil to have an anti-inflammatory effect, it has to be consumed in amounts greater than 14 g/d of ALA, which is equivalent to approximately 26 ml/d of flaxseed oil, a very large quantity.

Several case–control studies have associated consumption of ALA (flaxseed oil) with increased risk of developing prostate cancer.[94–96] In one follow-up study, men with the highest consumption of ALA had a 3.43-fold higher risk of advanced prostate cancer than those with the lowest consumption.[94] None of these studies are conclusive and none of the studies used flaxseed oil itself. Until better evidence is available, ALA supplements should be avoided in patients with prostate cancer or who are at risk of prostate cancer. Flaxseed oil may interact with anticoagulants, because of its antiplatelet aggregating effect, and hence precautions should be taken in patients who are already on anticoagulant therapy. Flax lignan appears to be safe for consumption. Limited evidence suggests that flaxseeds are better than flaxseed oil, and flax lignans are better than flaxseed for cardiovascular health.

CONCLUSION

Flaxseed, flaxseed with very low ALA, FLC, and SDG, but not flaxseed oil, suppress the development of atherosclerosis. FLC and SDG slow progression of atherosclerosis but do not regress atherosclerosis. Suppression of atherosclerosis by flaxseed is not the result of ALA, but is the result of the lignan content of flaxseed. The lipid-lowering effects of flaxseed are variable. However, flaxseed with very low ALA, SDG, and FLC significantly reduce serum lipids. SDG and FLC raise serum HDL-C. In general, flaxseed oil does not affect serum lipids. SDG is a very potent antioxidant and hypertensive agent. Flaxseed oil in high doses suppresses inflammatory mediators. Flaxseed oil decreases platelet aggregation and increases bleeding time. SDG is a potent angiogenic and antiapoptotic agent. Because of these attributes of flaxseed and its components, they may be effective in improving cardiovascular health.

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