Flaxseed and Cardiovascular Risk
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Flaxseed has recently gained attention in the area of cardiovascular disease primarily because it is the richest known source of both $\alpha$-linolenic acid (ALA) and the phytoestrogen, lignans, as well as being a good source of soluble fiber. Human studies have shown that flaxseed can modestly reduce serum total and low-density lipoprotein cholesterol concentrations, reduce postprandial glucose absorption, decrease some markers of inflammation, and raise serum levels of the omega-3 fatty acids, ALA and eicosapentaenoic acid. Data on the antiplatelet, antioxidant, and hypotensive effects of flaxseed, however, are inconclusive. More research is needed to define the role of this functional food in reducing cardiovascular risk.

Key words: flaxseed, lignans, $\alpha$-linolenic acid, cholesterol, cardiovascular disease

Introduction
Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in the United States. As part of a comprehensive strategy to reduce the burden of ASCVD, some investigators have proposed the incorporation of so-called “functional foods” such as nuts, fish, and soy protein into the diet. The National Cholesterol Education Program (NCEP) endorsed the use of plant sterols and soluble fiber to help lower serum cholesterol. Flaxseed is a functional food that has recently gained attention in the area of ASCVD prevention because it contains three key constituents: $\alpha$-linolenic acid (ALA), soluble fiber, and lignans. Flaxseed and flaxseed oil have been cited as potentially useful foods by the American Heart Association. The best evidence to date suggests that flaxseed products improve cardiovascular risk factors primarily by modestly improving lipid profiles; however, various components of flax have been shown to have antioxidant, anti-inflammatory, antiplatelet, hypoglycemic, and blood pressure–lowering properties. This review will focus on the bioactive components of flaxseed related to ASCVD prevention, the mechanisms by which flaxseed may reduce risk of ASCVD, and the animal and human clinical trial data regarding its safety and efficacy.

Historic Perspective
Evidence for flax cultivation can be found as early as 6000 BC when flax was first identified in Eastern Turkey to make cloth, known as linen. During the past millennia, components of flax have served a variety of uses throughout the world. Traditionally, the oil, known as linseed oil, was used as a drying agent in paint and varnish. The fiber of flax is well known for its use in fine linen clothing, while flaxseed meal is often used as an ingredient in animal feed and fertilizer. In present-day western societies, use of flaxseed in the human diet is growing because of its reported health benefits. According to the American Botanical Council, sales of flax products in 1999 increased by a remarkable 177%. Simultaneously, average sales for the top 20 selling botanicals fell by 3%. A more recent report in the lay press cited that flax sales were up by 23% in 2000 compared with the previous year.

Composition and Pharmacology
Flax (Linum usitatissimum) is a blue flowering crop that produces small, flat seeds that range in color from golden yellow to reddish brown. Flaxseed is commonly found as whole seed, ground seed (powder or meal), or flaxseed oil. The nutrient composition of the three forms of flax is described in Table 1. Flaxseed oil differs from whole and ground flaxseed by being devoid of both fiber and lignans. Whole flaxseed contains 41% fat, 28% dietary fiber, 21% protein, and minerals, vitamins, and carbohydrates. The oil in flaxseed is unique in that it is com-
posed of 73% polyunsaturated fatty acids (PUFA), 18% monounsaturated fatty acids (MUFA), and 9% saturated fatty acids, making it a low–saturated fat food.9 Flaxseed oil is the richest known source of the omega 3 (n-3) fatty acid, ALA, which comprises approximately 55% of the total fatty acids.10 Table 2 lists the foods that naturally contain the highest levels of ALA. The percent of fat as ALA in flaxseed is 5.5 times higher than that in the next-highest sources, walnuts and canola oil.

The dietary fiber portion of flax contains both insoluble and soluble fiber. At least some of the cardioprotective effects of flax are attributed to the soluble fiber known as mucilage (gum), which comprises approximately 25% of the total dietary fiber or an estimated 7 to 10% of full-fat flaxseed.10 Flaxseed also contains a large concentration of phytoestrogens called lignans. Plant lignans are phenolic compounds whose carbohydrate conjugate is removed by intestinal bacteria to form the bioactive mammalian lignans, enterodiol and enterolactone. These mammalian lignans are absorbed in the small intestine and conjugated in the liver. The conjugated lignans are excreted through the urine and bile and can undergo enterohepatic circulation, possibly promoting reabsorption. Flaxseed is the richest known source of the main mammalian lignan precursor, secoisolariciresinol diglucoside (SDG).12 Aside from flax, plant lignans are found in significantly lesser amounts (12–1500 times) in various fruits, vegetables, nuts, legumes, and grains (Table 3). Flaxseed also contains minor lignan components, including isolariciresinol, pinoresinol, and matairesinol.14 Human consumption of flaxseed increases urinary levels of enterodiol, enterolactone, and total lignans in a linear, dose-dependent manner.15

### Mechanisms of Action

Flax may protect against cardiovascular disease through a number of mechanisms, including reducing serum cholesterol, platelet aggregation, and inflammatory markers; improving glucose tolerance; and acting as an antioxidant.

### Effects of Fiber

Ways in which soluble fiber reduces total cholesterol and low-density lipoprotein cholesterol (LDL) have been previously reviewed and include enhanced gastric emptying, altered transit time, interference with bulk phase diffusion of fat, and increased excretion of bile acids.16 Flaxseed gum behaves like typical viscous fiber and may therefore decrease postprandial glucose absorption and improve glucose tolerance.17

### Effects of Lignans

Evidence also suggests that SDG may directly lower serum cholesterol.18 Lignans may be able to decrease
serum cholesterol by modulating the enzymes, $7\alpha$-hydroxylase and acyl CoA cholesterol transferase, both of which are involved in cholesterol metabolism. The lignans in flax may also reduce oxidative stress. SDG, enterodiol, and enterolactone have been shown to act as antioxidants by inhibiting peroxidation of PUFA in vitro at levels that may be achievable in vivo. Inhibiting peroxidation of PUFA may decrease oxidation of LDL, a key player in atherogenesis. Finally, SDG has been shown to act as an antagonist of platelet-activating factor.

**Effects of ALA**

ALA may prevent ASCVD through several mechanisms, including decreased inflammatory response, inhibition of platelet aggregation and thrombosis, decreased blood pressure, improved serum lipids, and prevention of cardiac arrhythmias. Extensive basic research on ALA and other omega-3 fatty acids suggests that they may protect against cardiovascular disease by interfering with production of proinflammatory and proaggregatory eicosanoids (prostaglandin E$_2$, thromboxane A$_X$, and leukotriene B$_4$). Both ALA and linoleic acid (LA, n-6) are essential fatty acids and therefore must be acquired through diet. Once consumed, LA and ALA can be converted to different fatty acids that yield different classes of the eicosanoids, which have different effects on inflammation, platelet aggregation, and vasoconstriction. LA can be converted to arachidonic acid (AA) through a series of alternating desaturation and elongation steps (Figure 1). By the same method, ALA can be converted to eicosapentaenoic acid (EPA) and perhaps docosahexaenoic acid (DHA), the fatty acids primarily found in cold-water marine fish. The metabolism of n-6 and n-3 fatty acids requires the same desaturation enzymes and thus the two are believed to be in competition. Because humans cannot interconvert n-3 and n-6 fatty acids, an excess of one class of PUFA can lead to the production of specific eicosanoids. Eicosanoids produced by EPA and DHA are involved with decreasing platelet aggregation, vasoconstriction, and thrombosis, whereas eicosanoids from AA produce the opposite effects.

Increasing dietary ALA, EPA, and DHA can reduce the ratio of n-6 to n-3 and thus enhance the biosynthesis of eicosanoids that are less inflammatory. Flaxseed oil has been shown to increase EPA levels in plasma phospholipids. The bioavailability of ALA from ground flaxseed is as high as from flaxseed oil. Beyond the effects of ALA on eicosanoid production, recent data suggests that dietary ALA may have additional physiologic effects related to atherogenic risk factors.

**Animal Data**

Animal studies have primarily focused on the question of whether flaxseed products can improve serum lipids; however, additional evidence is emerging as to the mechanism by which flax reduces risk of ASCVD.

Weanling rats fed 20% and 40% flaxseed for 90 days produced significantly lower serum total cholesterol and LDL levels than rats fed a diet devoid of flax. Prasad et al. reported that supplementing an antioxidant-free, 1% cholesterol diet (diet composition by weight: protein = 16.25%; fat = 3.77%; carbohydrates = 48.03%; dietary fiber = 14.65) with 7.5 g/kg of defatted flaxseed (2–3% ALA, but similar in lignan content to traditional flaxseed) significantly reduced total cholesterol and LDL in rabbits fed an atherogenic diet for 8 weeks when compared with controls, but the diet had no effect on high-density lipoprotein cholesterol (HDL). The authors concluded that ALA is not the responsible agent for reductions in total cholesterol and LDL seen with flaxseed administration. In a follow-up study, Prasad et al. found that adding purified SDG (15 mg/kg) to an atherogenic diet for 8 weeks in rabbits reduced total cholesterol and LDL by 33% and 35%, respectively, whereas it significantly increased HDL by $>140\%$ ($P<0.05$) in as few as 4 weeks. When the authors examined the extent of atherosclerotic burden in the aorta, the SDG-treated group had significantly smaller plaques and the lesions were distributed over a smaller area compared with the control group.

Prasad et al. also evaluated the in vivo antioxidant activity of flaxseed lignans in rabbits. They found that 7.5 g/kg regular flaxseed added to an antioxidant-free, basic chow diet with the addition of 1% cholesterol decreased atherosclerosis in the aorta by 46% and lowered the number of inflammatory polymorphonuclear leukocytes compared with the same diet without flax; however, the experimental diet had no effect on chole-
terol levels. When purified SDG (15 mg/kg) alone was added to an atherogenic diet for 8 weeks in rabbits, levels of aortic malondialdehyde (MDA, a lipid peroxidation product) were also reduced.30 MacDonald-Wicks et al. found that 40 female weanling Wistar rats fed 200 g flaxseed oil/kg body weight for 4 weeks produced the lowest 8-iso-PGF_2α plasma concentrations (an in vivo marker of oxidative stress) after administration of CCL_4 (an inducer of oxidative stress), compared with rats receiving saturated fat–containing or LA-containing diets.31 Limited animal evidence also suggests that components of flax may modestly improve blood pressure32 lower collagen-induced platelet aggregation,33 protect against developing type 1 diabetes,34 and retard development of type 2 diabetes.35

Human Studies
To identify the majority of human studies on the cardiovascular effects of flax, we performed a systematic search of the following databases: MEDLINE, BIOSIS Previews, CINHAL, Cochrane Collaboration Database, and PubMed. We used the MeSH headings “flax,” “alpha linolenic acid,” and “lignans,” and the search terms “flaxseed” and “linseed.” Using this strategy, we identified 360 relevant articles and book chapters. We also hand searched references from key review articles and chapters to identify previously missed references. The description below highlights the information on potential cardiovascular applications of flax products.

Epidemiologic Data
There are no available epidemiologic data concerning intake of flaxseed or flax-containing products and risk of ASCVD, most likely because there are no defined population groups that consume significant amounts of flax as part of a normal diet. There are, however, epidemiologic data relating to fiber, ALA, and lignans from other sources. Because flaxseed is a good source of soluble and insoluble fiber and the richest known dietary source of ALA and lignans, reviewing data from these studies is important; interpreting findings in relation to flaxseed, however, must be done with caution.

Epidemiologic data on fiber and risk of ASCVD are extensive and suggest in general an inverse association between total dietary fiber and risk of ASCVD.36 Several observational studies have found a positive association between ALA and primary37,38 and secondary prevention of ASCVD.39 In the Nurses’ Health Study, Hu et al. found a dose-response relationship between ALA intake and risk of ischemic heart disease, with a 45% reduction in risk of those consuming the highest levels of ALA.37 However, some results from observational studies conflict with these positive findings.40

Observational studies have also revealed that lignans may reduce ASCVD morbidity and mortality. Vanharanta et al. found that serum enterolactone concentrations, which indicate lignan intake, were inversely associated with risk of acute coronary events.41 After adjusting for the nine most strongly predictive risk factors, men in the highest enterolactone group had a 65.3% lower risk than men in the lowest quartile. Recently, these investigators found high serum enterolactone concentrations to be associated with reduced coronary heart disease and cardiovascular disease–related mortality in middle-aged Finnish men.42

Intervention Trial Data
Several secondary prevention trials involving ALA-enriched diets33,44 and supplemental ALA45 have implicated ALA as a cardioprotective nutrient; however, none of these studies used flax-specific sources so their generalizability to flax products is yet unknown. Published intervention studies using flax specifically have included whole and ground flaxseed as well as extracted flaxseed oil. The following sections describe data from human studies that address the effects of flax on various areas of cardiovascular risk, including lipids, inflammation, platelet aggregation, oxidation stress, blood pressure, and glucose metabolism.

Hypolipidemic Effects
The bulk of the evidence from nine clinical trials suggests that whole flaxseed or its powder (15–50 g/day) can modestly reduce total cholesterol and LDL by 1.6 to 18% in both hypercholesterolemic46–50 and normocholesterolemic51,52 patients without a significant effect on HDL or triglycerides (TG) (Table 4). The results have not all been consistent, however, with two most recent trials showing no significant effect of flaxseed on LDL in healthy patients with hypercholesterolemia.50,53 Data on extracted flaxseed oil is much less consistent, with a few studies finding a modest reduction in TG with large doses (60 mL or ~4 tablespoons/day), but most finding no effect.54 Flaxseed oil given alone does not appear to have any beneficial effects on total cholesterol, LDL, or HDL.54 While there are no human studies investigating the effects of extracted flax lignans on lipids, Kuroda et al. evaluated the lipid effects of a series of synthetic lignans (arylnaphthalene lignans), and reported they significantly lower TC and LDL and raise HDL.55

The results from these studies are summarized in Table 4, with several of the largest trials discussed below. Arjmandi et al. conducted a double-blind, randomized, crossover trial to compare the lipid effects of whole flaxseed with sunflower seed (control) in 38 moderately hyperlipidemic postmenopausal women (mean baseline LDL = 4.09 mmol/L).49 Subjects were randomly assigned to receive 38 g of either whole flaxseed or whole sunflower seed baked into breads and/or muf-
### Table 4. Clinical Trials Reporting Lipid Effects of Ground or Whole Flaxseed

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Patient Population (Sample Size)</th>
<th>Intervention</th>
<th>Treatment Duration</th>
<th>Comparator Group</th>
<th>% Change in TC</th>
<th>% Change in LDL</th>
<th>% Change in HDL</th>
<th>% Change in TG</th>
<th>Other Cardiovascular Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bierenbaum et al.46</td>
<td>Uncontrolled trial</td>
<td>Hypercholesterolemic adults (n = 15)</td>
<td>15 g ground flaxseed and 3 slices of 10% flax-containing bread, vitamin E 800 IU alone</td>
<td>3 months</td>
<td>Vitamin E 800 IU alone</td>
<td>↓ 6.7%*</td>
<td>↓ 10%*</td>
<td>↓ 2% (NS)</td>
<td>↑ 11.7% (NS)</td>
<td>Inconsistent findings on platelet aggregation</td>
</tr>
<tr>
<td>Cunnane et al.26</td>
<td>Uncontrolled trial</td>
<td>Healthy women (n = 9)</td>
<td>50 g flaxseed provided as supplement or in baked bread</td>
<td>4 weeks</td>
<td>None</td>
<td>↓ 9%*</td>
<td>↓ 18%*</td>
<td>No change</td>
<td>No change</td>
<td>Postprandial glucose ↓ 27%*</td>
</tr>
<tr>
<td>Clark et al.47</td>
<td>Uncontrolled trial</td>
<td>Adults with lupus nephritis and hypercholesterolemia (n = 8)</td>
<td>15, 30, and 45 g flaxseed for 4 weeks at each dose</td>
<td>12 weeks</td>
<td>No control</td>
<td>↓ 11% at 30 and 45 g</td>
<td>↓ 12% at 30 g and 45 g</td>
<td>↓ 6.3% at 45 g (NS)</td>
<td>↓ 3.7% at 45 g (NS)</td>
<td>PAF-induced platelet aggregation inhibited at all doses</td>
</tr>
<tr>
<td>Cunnane et al.51</td>
<td>RCT crossover</td>
<td>Healthy young adults (n = 10)</td>
<td>50 g flaxseed provided as muffins</td>
<td>4 weeks</td>
<td>Wheat bran muffins</td>
<td>↓ 5%</td>
<td>↓ 8%</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Arjmandi et al.49</td>
<td>RCT crossover</td>
<td>Hypercholesterolemic, postmenopausal women (n = 38)</td>
<td>38 g whole seeds baked into breads and muffins</td>
<td>6 weeks</td>
<td>Sunflower seed in breads and muffins</td>
<td>↓ 6% (NS)</td>
<td>↓ 14.7%*</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Jenkins et al.48</td>
<td>RCT crossover</td>
<td>Hypercholesterolemic adults (n = 29)</td>
<td>50 g partially defatted flaxseed in muffins</td>
<td>6 weeks</td>
<td>Wheat bran muffins</td>
<td>↓ 4.6%*</td>
<td>↓ 7.6%*</td>
<td>↓ 1.4% (NS)</td>
<td>↑ 10.2%†</td>
<td>Apo B ↓ 5.4%‡ Apo A-1 ↓ 5.8%‡</td>
</tr>
<tr>
<td>Clark et al.52</td>
<td>RCT crossover</td>
<td>Adults with lupus nephritis (n = 23)</td>
<td>30 g ground flaxseed to be added to food</td>
<td>1 year</td>
<td>No control</td>
<td>No change</td>
<td>No change</td>
<td>↑ 3% (NS)</td>
<td>No change</td>
<td>9 patients adherent to flaxseed</td>
</tr>
<tr>
<td>Lucas et al.50</td>
<td>RCT parallel</td>
<td>Postmenopausal women (n = 58)</td>
<td>40 g ground seed mixed into foods of choice</td>
<td>3 months</td>
<td>Wheat bran</td>
<td>↓ 6%</td>
<td>↓ 4.7% (NS)</td>
<td>↓ 4.7% (NS)</td>
<td>↓ 12.8% (NS)</td>
<td>Apo A-1 ↓ 9% Apo B ↓ 7.5%‡</td>
</tr>
<tr>
<td>Lemay et al.53</td>
<td>RCT crossover</td>
<td>Postmenopausal hypercholesterolemic women (n = 25)</td>
<td>40 g ground seed provided both in bread and ground seed</td>
<td>2 months</td>
<td>Hormone replacement therapy (CEE ± progestins)</td>
<td>↓ 2.8% (NS)</td>
<td>↓ 1.6% (NS)</td>
<td>↓ 7.1% (NS)</td>
<td>↓ 1.2% (NS)</td>
<td>Flax ↓ blood glucose by 5.3%; ↑ insulin by 10.7% (NS)</td>
</tr>
</tbody>
</table>

*P < 0.01
†P < 0.05
‡P < 0.001
§P < 0.005

PAF = platelet-activating factor NS = non-significant (P ≥ 0.05), RCT = randomized, controlled trial, CEE = Conjugated Equine Estrogen, TC = total cholesterol, LDL = low-density lipoprotein, HDL = high-density lipoprotein, TG = triglyceride.
fins for 6 weeks. At the end of 6 weeks, subjects entered a 2-week washout period and then received the other treatment regimen for the remaining 6 weeks. Researchers found a 14.7% (P < 0.001) reduction in LDL in the flax-treated group compared with the sunflower control period. There were no effects on TG or HDL, but lipoprotein(a), a novel marker of coronary heart disease, was mildly but consistently reduced by 7.4%. The LDL results in this study were impressive, but may have been influenced by limitations of this study. The researchers did not report potential differences in dietary saturated fat intake between treatment periods, which might have confounded the results. In addition, the small number of patients (n = 38) and the specific study population (postmenopausal women) make it difficult to draw definitive conclusions.

Jenkins et al. compared the effects of 50 g partially defatted flaxseed (removing the ALA) with a wheat bran control over a 3-week treatment period in 29 hyperlipidemic (mean LDL = 4.40 mmol/L) subjects (22 men and 7 postmenopausal women) in a randomized, crossover study. Both flaxseed and wheat were provided in the form of muffins. Subjects were instructed to follow the NCEP step II diet throughout the entire study. Flaxseed treatment significantly lowered total cholesterol (−4.6 ± 1.2%; P = 0.001), LDL (−7.6 ± 1.8%; P < 0.001), apolipoprotein B (−5.4 ± 1.4%; P = 0.001), and apolipoprotein A-I (−5.8 ± 1.9%; P = 0.005). Whereas flaxseed did significantly lower apolipoprotein A-I concentrations, there was no significant change in HDL. These results from this short-term study suggest that the hypocholesterolemic effects of flaxseed are most likely due to the fiber, lignans, or the combination of these two constituents.

Whereas these two studies suggest a LDL-lowering effect, two larger, longer, and more recent studies have failed to confirm the hypocholesterolemic effect of flaxseed. Lucas et al. examined the effects of 40 g ground flaxseed on lipid metabolism in 58 postmenopausal women not on hormone replacement therapy (HRT). These normal lipidemic women (mean LDL = 3.21 mmol/L, mean HDL = 1.89 mmol/L) were randomly assigned to receive daily 40 g of either ground flaxseed or a wheat-based control in a parallel design over 3 months. Flaxseed reduced LDL by 4.7% and TG by 12.8%, but did not reach a level of significance compared to the wheat control. LDL findings may be explained by the low level of hypercholesterolemia and the small sample size for a parallel design. While LDL and TG were not altered by flax, total cholesterol and non-HDL cholesterol decreased significantly (P < 0.05) by 6% in flax-treated subjects compared to the wheat-treated group. Finally, Lemay et al. used a crossover design to study the effects of 40 g/day of crushed flaxseed over 2 months in postmenopausal women. These authors compared women receiving flaxseed with women on HRT, an active control. While HRT had predictable and expected lipid-modulating properties (HDL increased by 11% and LDL decreased by 16%), flaxseed had no significant effect on any lipid parameter. Interestingly, both flaxseed and HRT reduced vasomotor symptoms equally in this population. Thus, while the majority of published intervention studies suggest an LDL-lowering effect of moderate doses of flaxseed supplementation, questions remain about the consistency and duration of this effect. Future studies will need to clarify the lipid effects of flax in more varied populations (men and premenopausal women).

**Anti-inflammatory and Antiplatelet Effects**

Because it is widely recognized that atherosclerosis is an inflammatory disorder, there has been much interest in the effects of n-3 fatty acids on markers of inflammation. Most of the available data is on the effects of EPA and DHA from fish oils rather than on those of the precursor, ALA. Caughey et al. investigated the effects of a flaxseed oil–based diet on tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β) synthesis in healthy subjects. After incorporation of approximately 14 g ALA from flaxseed oil into the diet for 4 weeks, TNF-α and IL-1β production decreased by approximately 30% by lipopolysaccharide (LPS)-stimulated mononuclear cells. Another study found that 2 g of ALA from flaxseed oil did not change circulating cytokine levels or numbers of inflammatory cells in healthy adults. There was, however, a reduction in soluble vascular cell adhesion molecule 1 and soluble E-selectin, both of which are markers of endothelial activation, in the flaxseed oil–treated group. A more recent study found that low doses of isolated ALA (3.5 g/d) from flaxseed oil supplied as capsules for 12 weeks did not affect cytokine production, mononuclear cell subsets, or lymphocyte proliferation.

While epidemiologic data point to a potential platelet inhibitory effect of ALA, human studies have not shown a consistent antiplatelet effect. One study found that flaxseed powder and flaxseed bread improved one measure of platelet adhesion. Allman et al. reported that 40 g of flaxseed oil over 23 days produced an increase in the platelet EPA:AA ratio (a marker for thromboxane production and platelet aggregation potential), which suggests that flaxseed oil may decrease the tendency of platelets to aggregate. A study of 29 healthy subjects randomized to receive 5.9 g/day of flaxseed oil or 5.2 g/day of fish oil found that both treatments modestly reduced adenosine diphosphate (ADP)-induced platelet aggregation without a significant difference between groups. However, a larger and more recent study used multiple different methods and did not find an antiplatelet effect of low- or high-dose...
flaxseed oil.62 In addition, this study found no changes in bleeding time, prothrombin time, or fibrinogen.

**Antioxidant Effects**
Results from human intervention studies reveal either no antioxidant effects26 or a potential deleterious increase of ex vivo markers of oxidative stress after flaxseed consumption.48,63 Ex vivo measures of oxidative stress, including the popular thiobarbituric acid–reactive substances, however, have been criticized because of their lack of specificity.64 The in vivo measurement of F₂-isoprostanes, non-enzymatic free radical oxidation products of arachidonic acid that reflect oxidative damage of tissues, have allowed for more accurate evaluation of oxidative stress. Using this technique, a recent epidemiologic study found an inverse association of serum enterolactone to plasma F₂-isoprostane concentrations.65 More research from intervention trials is clearly needed to evaluate the effect of flaxseed on these in vivo measures of oxidative stress.

**Hypotensive Effects**
The evidence for a hypotensive effect of flax or its components is unconvincing. Two observational studies in more than 500 patients suggest that dietary and tissue ALA correlate with lowered blood pressure.66,67 In one study, a regression analysis found that for each 1% increase in tissue ALA, mean arterial blood pressure decreased by 5 mm Hg.67 Another observational study also found that serum enterolactone concentrations were inversely associated with blood pressure.41 Despite limited animal evidence of favorable blood pressure effects,68 no human clinical trials have reported a hypotensive effect of flaxseed or its components. A study by Kestin et al. compared 9.2 g of ALA from flaxseed oil with 3.4 g of EPA and DHA from fish oil in 39 normotensive adults.69 At the end of 6 weeks, only the fish oil–supplemented diet lowered systolic blood pressure by 5 mm Hg. Finally, a small clinical trial in 15 obese patients found that 20 g/day of ALA from flaxseed oil had no effect on blood pressure, but did increase systemic arterial compliance (a measure of endothelial function) compared with an oleic acid–enriched diet.63

**Effects on Glucose Metabolism**
Data from two clinical trials suggest flaxseed may improve glucose homeostasis.26 In the first of two experiments by Cunnane et al., six volunteers (after an overnight fast) consumed 50 g of carbohydrates from bread made with either flaxseed or wheat flour. Blood glucose samples were obtained at baseline and 15, 30, 45, and 60 minutes after starting to consume the meal. The authors found a 28% reduction in the area under the curve for serum glucose in those consuming flax compared with those consuming wheat. In a separate experiment, soluble fiber extracted from flaxseed reduced glucose absorption by 27%.26 Lemay et al. found 40 g ground flaxseed added to the diet of postmenopausal women for 2 months significantly reduced blood glucose (−5.3%) (P <0.05) from baseline. Flaxseed also reduced insulin levels by 10.7% compared with baseline, but this finding did not reach statistical significance.53 A study by McManus et al. revealed no effect of n-3 fatty acids from flaxseed oil on HbA1c, fasting glucose, or insulin levels in patients with well-controlled type 2 diabetes.70 Findings from these limited studies suggest that flax meal improves insulin sensitivity, likely because of its soluble fiber content, which may delay postprandial glucose absorption in the gut.

**Adverse Effects of Flaxseed-containing Products**
Anaphylactic episodes as a result of flaxseed hypersensitivity have been reported.71 The U.S. Food and Drug Administration allows inclusion of up to 12% (by weight) flaxseed in foods, but flaxseed meal and cold-pressed flaxseed oil have not yet attained Generally Recognized as Safe (GRAS) status. For individuals who are not allergic to flaxseed, potential problems with the fiber and lignan components of flax could still occur. Whereas human studies using up to 50 g flaxseed per day for up to one month revealed no adverse effects and were well tolerated, researchers found a 30% increase in bowel movements.51

Lignans in flax have structural and functional similarities to the human estrogen, 17β-estradiol and thus may alter hormone metabolism. Human studies examining the effects of ground or whole flaxseed on endocrine function are limited, but suggest flax may reduce serum concentrations of 17β-estradiol and estriol sulfate and increase prolactin levels in postmenopausal,12 but not in menstruating women.72 Furthermore, flaxseed has been shown to reduce total testosterone and free androgen index levels in men with prostate cancer.73 Owing to these biologic effects, use of lignans in preventing and treating hormone-dependent cancers as well as serving as an alternative to traditional estrogen replacement therapy for the treatment of menopausal systems is being investigated. While flax may be promising in these populations, the multiple and complex actions of flax creates a potential risk of adverse effects if ingested in large amounts.

There is no published evidence concerning the safety of flax in pregnancy and lactation or in children; however, in rats, high levels of flaxseed (10% diet) resulted in lower birth weight (P <0.05) and produced hormonal effects in both males and females.74 A final concern exists with consuming uncooked flaxseed due to the production of cyanogenic glycosides.
(HCN), which in large doses can be toxic to animals and humans. Use of high doses of uncooked flaxseed meal (>10 Tbsp/day) may raise HCN levels above 50 to 60 mg of inorganic cyanide, which is considered potentially toxic in adults.75 Data to date, however, suggests that doses of up to 50 g/day of baked flaxseed powder do not increase urinary thiocyanate levels.26 There have been no reported cases of acute or chronic cyanide toxicity from flaxseed consumption, and baking flaxseed removes this theoretical risk.

**Conclusion**

Daily consumption of 15 to 50 g of ground flaxseed meal (1–5 Tbsp/day) can modestly reduce total cholesterol and LDL concentrations without significantly altering TG or HDL. The exact mechanism is unclear, but studies to date point to the soluble fiber and/or lignan as the hypocholesterolemic components of flaxseed. Flaxseed oil does not seem to have an effect on cholesterol concentrations, but may reduce TG when consumed in large, impractical doses. In addition, flaxseed oil does not contain soluble fiber or lignans, which may also be beneficial in improving glucose homeostasis and serving as antioxidants, respectively. However, replacing flaxseed oil for oils that contain low levels of ALA, such as safflower or corn oil, can provide the required amounts of ALA, a strategy that may lower risk of clinical cardiovascular disease. While initial data on the effectiveness of flaxseed products in improving ASCVD risk seems promising, randomized, controlled clinical trials are needed to establish the safety and efficacy of long-term flaxseed ingestion on a wider array of cardiovascular surrogate markers. Only then can larger clinical endpoint studies be planned using this promising functional food.

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