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# Flaxseed and Flaxseed Oil for Cardiovascular Disease: Beyond Lowering Cholesterol

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## Flaxseed and Flaxseed Oil for Cardiovascular Disease: Beyond Lowering Cholesterol

### Part II Of A Series on Flaxseed

*By Philippe O. Szapary MD, and LeAnne T. Bloedon, MS, RD*

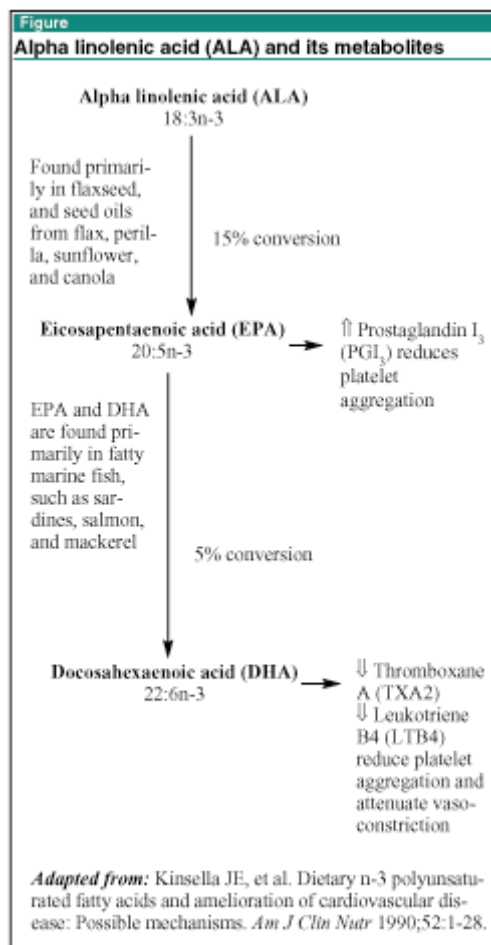
The popularity of flax—and sales are booming—stems in part from the fact that it contains three important constituents: soluble fiber, alpha linolenic acid (ALA), and lignans. These have all been implicated in the prevention and treatment of cardiovascular disease (CVD).

Flaxseed products appear to improve cardiovascular risk factors primarily by modestly improving lipid profiles.<sup>1</sup> Because flaxseed is rich in both ALA and lignans, flax also might modulate cardiovascular risk factors by other mechanisms (e.g., reducing oxidant stress, platelet adhesion, blood sugar, and blood pressure).

### Composition and Pharmacology

Flaxseed commonly is found as whole seed, ground seed (meal), or flaxseed oil. Whole flaxseed contains 41% fat, 28% dietary fiber, and 21% protein, in addition to minerals and vitamins.<sup>2</sup> The oil is comprised of 73% polyunsaturated fatty acids, 18% monounsaturated fatty acids, and 9% saturated fatty acids, making it a low saturated fat food.<sup>2</sup>

Flax is the richest known source of ALA,<sup>3</sup> which is a cardioprotective polyunsaturated fatty acid and the precursor to omega-3 fatty acid. Between 5% and 10% of ALA is converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the fatty acids found in cold water marine fish.<sup>4</sup> EPA and DHA then are converted into a series of eicosanoids that favorably affect inflammation, vasoconstriction, and platelet aggregation (*see Figure, below*).



Flaxseed also is a good source of soluble fiber (mucilage), which is believed to be partially responsible for its potential blood glucose-lowering effects.<sup>3</sup> About a third of the fiber in flax is soluble (or viscous) fiber, second only to psyllium seed.

Flaxseed contains several phytoestrogenic lignans, and is the richest source of the main mammalian lignan precursor, secoisolariciresinol (SDG). The levels of SDG in flaxseed meal vary between 0.6 g and 1.8 g/ 100 g.<sup>5</sup> Once ingested, SDG is metabolized by enteric bacteria to form the bioactive mammalian lignan, enterodiol, which then can be oxidized to enterolactone. Structurally, enterodiol and enterolactone share features with both estrogen and the selective estrogen receptor modulator, tamoxifen.

## Mechanisms of Action

The active components of flax—ALA, soluble fiber, and lignans—each have different mechanisms.

Extensive basic research on ALA and other omega-3 fatty acids suggests that they may protect against CVD by interfering with production of classical "2 series" prostaglandins as well as thromboxanes and leukotrienes, which promote platelet aggregation, vasoconstriction, and thrombosis.<sup>6</sup> ALA also may protect against CVD by increasing the ALA content of membrane phospholipids, which results in changes that influence calcium ion exchange across the cell membrane.<sup>7</sup> Anti-arrhythmic effects of EPA and DHA, ALA derivatives, have been shown in in vitro and in vivo animals studies.<sup>8</sup>

Soluble fiber is well known to reduce postprandial glucose absorption and hyperinsulinemia.<sup>9</sup>

Lignans in flax possess antioxidant properties. SDG, enterodiol, and enterolactone inhibit peroxidation of polyunsaturated fatty acids in vitro.<sup>10,11</sup> SDG also has been shown to act as an antagonist of platelet-activating factor and thus may affect platelet aggregation.<sup>12</sup>

## **Animal Studies**

Prasad found that flax added to a 1% cholesterol diet in rabbits decreased aortic atherosclerosis by 46% and lowered polymorphonuclear leukocyte counts (PMNLs).<sup>10</sup> PMNLs enhance production of oxygen free radicals, which have been implicated in the development of atherosclerosis.

## **Human Studies**

We performed a systematic search of the following databases: MEDLINE, BIOSIS Previews, CINHALL, Cochrane Collaboration Database, and CAM on PubMed. We used the MeSH headings "flax," "alpha linolenic acid," "fatty acid, omega-3," "lignans," "dietary fiber," as well as the search terms flaxseed and linseed. Using this strategy, we identified 353 articles and book chapters. The description below highlights the information specifically on non-lipid cardiovascular applications of flax products.

*Direct cardioprotective effect.* Both population-based, case-control studies and cohort studies have found that those who consume foods with the most ALA have the lowest incidence of both fatal and non-fatal cardiac events.<sup>13,14</sup>

The Lyon Diet Heart study is the only intervention study that supports the direct cardioprotective benefits of ALA.<sup>15</sup> In this study, 605 French post-myocardial infarction patients were randomized to either a Mediterranean type diet or a control diet and then followed for five years. The study was stopped early when a remarkable 76% relative risk reduction in cardiac death was attributed to the Mediterranean diet. There were 20 cardiac deaths in the control group vs. three in the experimental group (P = 0.02).

The benefit of the Mediterranean diet was largely attributed to the higher ALA content (primarily from a canola-enriched test margarine), but the two arms also differed in their vitamin C and E content and their cholesterol level.

Separately, one case-control study has shown that higher serum levels of enterolactone lower the risk of acute coronary events, raising the possibility that the lignan component of flax may have cardioprotective effects.<sup>16</sup> There are no published cardiac intervention trials in which supplemental ALA or SDG derived from flax have been tested.

*Hypotensive effects.* Two observational studies in more than 500 patients suggest that both dietary and tissue levels of ALA are correlated with lowered blood pressure,<sup>17,18</sup> yet clinical trials do not report a hypotensive effect. One study compared 9.2 g of ALA from flaxseed oil to 3.4 g of EPA and DHA from fish oil in 39 normotensive adults.<sup>19</sup> At the end of six weeks, only the fish oil-supplemented diet lowered systolic blood pressure, by 5 mm Hg.

*Antioxidant and antiplatelet effects.* Results from human studies revealed either no in vitro antioxidant effect<sup>3</sup> or a potential deleterious increase of in vitro markers of oxidant stress.<sup>20</sup> However, there are no current published human studies that investigate in vivo measures of oxidant stress. Epidemiolog-

ic data point to a potential platelet inhibitory effect of ALA;<sup>21</sup> however, human interventional studies have not shown a consistent antiplatelet effect.

*Effects on glucose handling.* To date, only one small published study has suggested that flaxseed may improve glucose homeostasis.<sup>3</sup> In this study, six volunteers consumed 50 g of carbohydrates from bread either made with flaxseed or wheat flour. The authors found a 28% reduction in the area under the curve for serum glucose absorption with flax compared to wheat. In a separate experiment, soluble fiber extracted from flax reduced glucose absorption by 27%.<sup>3</sup> In aggregate, these results suggest that flax meal does delay glucose absorption, and that this is most likely due to the non-specific effects of the soluble fiber.

## **Adverse Effects and Drug Interactions**

Anaphylactic episodes as a result of flaxseed hypersensitivity have been reported.<sup>22</sup> The 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 GRAS (Generally Recognized as Safe) status.

Although 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.<sup>23</sup> Additionally, the small whole flaxseeds theoretically could precipitate a bout of diverticulitis and probably should be avoided by patients with known diverticular disease. Grinding the seeds should remove this theoretical risk and improve the bioavailability of both ALA and lignans.

There is no published evidence concerning the safety of flax in pregnancy, lactation, or children. However, flax has potential hormonal effects, which may result from lignans binding to estrogen receptors. Animal data suggest some adverse effects of flaxseed and isolated SDG on pregnancy outcomes.<sup>24</sup> Data to support a hormonal effect of lignans from flaxseed in humans come from studies showing changes in levels of serum sex hormones.<sup>25</sup>

A potential concern with uncooked flaxseed meal is the production of cyanogenic glycosides (HCN), which in large doses can be toxic to animals and humans. Doses of up to 50 g/d of baked flaxseed powder do not increase urinary thiocyanate levels.<sup>3</sup> Use of high doses of uncooked flaxseed meal (> 10 tbsp/d) may raise HCN levels above 50-60 mg of inorganic cyanide, which is considered potentially toxic in adults.<sup>26</sup> There have been no reported cases of acute or chronic cyanide toxicity from flaxseed consumption, and baking flaxseed removes this theoretical risk.

## **Dosage**

Four tablespoons of flaxseed meal (180 kcal) deliver about 2 g of soluble fiber, and also provide approximately 600 mg of EPA (converted from 6 g ALA), which is estimated to be a cardioprotective dose in high-risk patients. A daily dose of 1 tbsp of oil would provide the necessary amount of omega-3 fatty acids, with slightly fewer calories (about 120 kcal), yet has no soluble fiber or lignans.

## **Dietary Sources of Flax**

Flaxseed is available in health food stores and some grocery stores where it is sold as whole seed or ground into a coarse powder (*see Table, below*). Flaxseed oil is available in many vitamin shops where it is found in both capsule and liquid form. The oil is best used in salad dressings where it can replace other vegetable oils.

## Table

### Comparison of commercially available flaxseed products

Product	ALA Content	Dietary Fiber	Lignans	Calories	Price
Flaxseed Meal (Forti-Flax, Barlean's)	1.5 g/tbsp	1.5 g/tbsp	Yes (> 50 mg)	45 kcal/tbsp	\$7.95/16 oz
Flaxseed Oil (Barlean's)	7.7 g/tbsp	0	No	120 kcal/tbsp	\$7.50/8 oz
Omega-3 eggs (Wilcox Farms)	525 mg/large egg	0	No	Not listed	\$2.00/10 eggs

**Sources:** Nutrient labels on the products

Flaxseed meal often is used in baking (e.g., muffins, bread, and cookies) or mixed into other foods (e.g., yogurt, hummus, salads, and juices). These functional foods may become an important non-fish source of omega-3 fatty acids. The meal can remain fresh for approximately three months in the refrigerator or six months in the freezer.

The oil becomes rancid quickly when exposed to heat, light, or oxygen, and thus must be stored in an opaque bottle and refrigerated after opening.

ALA-enriched eggs have been available in Canada and Europe and now are becoming more widely available in the United States. Laying hens are fed a diet high in flaxseed powder, which increases the yolk content of ALA and DHA without altering cholesterol content.

## Conclusion

Whole and ground flaxseed and flaxseed oil are excellent sources of ALA. All may be part of a cardioprotective diet, especially in high-risk patients. Flaxseed meal has several advantages over the oil and whole seed. Meal, but not oil, contains soluble fiber, which may improve glucose homeostasis in patients with Type 2 diabetes or those with impaired glucose tolerance, if used as part of a high-fiber

diet. Ground flaxseed contains lignans, although the oil does not, and they may contribute to the antioxidant properties of this functional food. Flax meal allows fiber, ALA, and lignans to be more easily bioavailable than does whole flax seed.

Randomized trials of specific flaxseed products should fully investigate the role of this functional food in reducing the risk of cardiac events, and in understanding the hormonal effects of long-term lignan consumption.

## Recommendation

Patients at high risk of cardiovascular disease should consider incorporating 25-50 g (3-6 tbsp) of flaxseed meal per day into a low saturated fat (< 7%), high-fiber (> 8 g soluble fiber), plant-centered diet as recommended by the National Cholesterol Education Program and World Health Organization. Alternatively, 1-2 tbsp of flaxseed oil can be substituted for other vegetable oils in high-risk patients who do not choose to eat cold water marine fish regularly. Flax-based products should not, at this point, be recommended for their antiplatelet, antioxidant, or blood pressure-lowering effects.

*Dr. Szapary is Assistant Professor in the Division of General Internal Medicine and in the Cardiovascular Risk Intervention Program; Ms. Bloeden is Project Manager in the Cardiovascular Risk Intervention Program, University of Pennsylvania Health System, in Philadelphia.*

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