Published in final edited form as:
Nutr Rev. 2010 October ; 68(10): 571–603. doi:10.1111/j.1753-4887.2010.00319.x.

Dietary lignans: physiology and potential for cardiovascular disease risk reduction

Julia Peterson[1], **Johanna Dwyer**[1,2], **Herman Adlercreutz**[3], **Augustin Scalbert**[4], **Paul Jacques**[1], and **Marjorie L McCullough**[5]

[1]Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging and Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA [2]School of Medicine, Tufts University and Frances Stern Nutrition Center, Tufts Medical Center, Boston, MA [3]Institute for Preventive Medicine, Nutrition, and Cancer, Folkhälsan Research Center, Biomedicum, and Division of Clinical Chemistry, University of Helsinki, Finland [4]Unité de Nutrition Humaine INRA Centre de Recherche de Clermont-Ferrand/Theix 63122 Saint-Genes-Champanelle France [5]Epidemiology Research Program, American Cancer Society, Atlanta, GA

Abstract

We reviewed lignan physiology and lignan intervention and epidemiological studies to determine if they decreased the risks of cardiovascular disease in Western populations. Five intervention studies using flaxseed lignan supplements indicated beneficial associations with C-reactive protein and a meta-analysis, which included these studies, also suggested a lowering effect on plasma total and low-density lipoprotein cholesterol. Three intervention studies using sesamin supplements indicated possible lipid and blood pressure lowering associations. Eleven human observational epidemiological studies examined dietary intakes of lignans in relation to cardiovascular disease risk. Five showed decreased risk with either increasing dietary intakes of lignans or increased levels of serum enterolactone (an enterolignan used as a biomarker of lignan intake), five studies were of borderline significance, and one was null. The associations between lignans and decreased risk of cardiovascular disease are promising, but are yet not well established, perhaps due to low lignan intakes in habitual Western diets. At the higher doses used in intervention studies, associations were more evident.

Keywords

lignans; cardiovascular disease; review

Introduction

The lignans are bioactive, non-nutrient, non-caloric phenolic plant compounds that are found in highest concentration in flax and sesame seeds and in lower concentrations in grains, other seeds, fruits and vegetables. The enterolignans (sometimes referred to as mammalian lignans) are metabolites of food lignans produced by human intestinal bacteria. They have been identified in human urine and plasma. Their weak estrogenic[1] and other biochemical properties suggest potential for nutritional significance in the prevention of cardiovascular and other chronic diseases.[2-4] This article briefly describes the chemistry and biosynthesis

Correspondence: Johanna Dwyer, DSc, RD, Director, Frances Stern Nutrition Center, Tufts Medical Center, 800 Washington St. Box 783, Boston, MA 02111, T (617) 636-5273, F (617) 636-8325, jdwyer1@tuftsmedicalcenter.org.

Conflict of Interest: None

of lignans in plants (including flaxseed and sesame), major food sources, their metabolism in humans, and recent studies of their associations with cardiovascular disease biomarkers, events and mortality in humans.

Chemistry and occurrence of lignans

Monolignols (Figure 1a), derived from hydroxycinnamic acids (*p*-coumaric, ferulic, and sinapic acids), are either dimerized to *lignans* (Figure 1b) in the cell or polymerized into larger lignin structures in the cell wall (Figure 1c). These structurally diverse compounds are involved in plant defense (as antioxidants, biocides, phytoalexins, etc.),[5] providing protection against diseases and pests, and possibly participating in plant growth control.[6,7]

Lignans and lignins are very different and should not be confused with each other. *Lignans* are stereospecific dimers of these cinnamic alcohols (monolignols) bonded at carbon 8 (C_8-C_8) (Figure 1b).[8]

In the plant, *lignans* (monolignol dimers) usually occur free or bound to sugars.[6,7] Diglucosides of pinoresinol, secoisolariciresinol, and syringaresinol are common.[9-12] Sesaminol triglucoside and sesaminol diglucoside occur in sesame seeds.[13-15] In flax, secoisolariciresinol is present as a diglucoside and is part of an ester-linked complex or oligomer (Figure 2) containing 3-hydroxyl-3-methylglutaric acid, a number of cinnamic acid glycosides (usually ferulic or *p*-coumaric acid) and the flavonoid herbacetin.[16-21]

The plant *lignans* most commonly distributed in foods are lariciresinol, mataireSinol, pinoresinol, and secoisolariciresinol (Figure 3). Several other lignans are present in some foods, including medioresinol (in sesame seeds, rye, and lemons), syringaresinol (in grains), sesamin and the lignan precursor sesamolin (in sesame seeds)[12,22] (Figure 3). Other lignans found in foods but not often quantified include arctigenin, cyclolariciresinol (isolariciresinol), 7′-hydroxymatairesinol, and 7-hydroxysecoisolariciresinol.[2,12] (Some cyclolariciresinol occurs naturally and some is formed from lariciresinol during extraction and analysis under acidic conditions.) The nutritional significance of lignans is unknown. Although *lignans* are not classified as dietary fibers, they share some of the chemical characteristics of lignin, which is an insoluble fiber.[23]

Lignins are large plant polymers built from the *p*-coumaryl, coniferyl, and sinapyl hydroxycinnamic alcohols (see Figure 1c). They are racemic (non-stereospecific) polymers, with monolignol units binding at C_8 and four other sites (C_5-C_5, C_5-C_8, C_5-*O*-C_4, C_8-*O*-C_4).[24] *Lignins* are found in vessels and secondary tissues of all higher plants. They are present in a large variety of foods and are particularly abundant in cereal brans.[25] Nutritionally lignins are considered components of insoluble dietary fiber.[26] Lignins are important in plants because they strengthen the plant cell walls, aid water transport, keep polysaccharides in the plant cell walls from degrading, help plants resist pathogens and other threats, and provide texture in edible plants.[24]

Food sources of lignans

The lignan content of foods is generally low and usually does not exceed 2 mg/100 g. The exceptions are flaxseed[27] (335 mg/100g) and sesame seeds (373 mg/100g),[22,28] which have a lignan content a hundred times higher than other dietary sources.

Table 1 provides examples of the distribution of lignans in foods.[10,12,28-35] They are present in many plant families, although the types and amounts vary from one family to another. Lignans are found in whole grains (especially in the bran layer) and seeds (in the seed coat). Barley, buckwheat, flax, millet, oats, rye, sesame seeds and wheat contain fairly high levels

of lignans. Nuts and legumes are also reasonably good sources. Although in lesser amounts than in grains, lignans are also present in fruits and vegetables such as asparagus, grapes, kiwi fruit, lemons, oranges, pineapple, wine and even in coffee and tea.[12,29-32]

In contrast to plants, there are virtually no lignans in animal foods. Minute amounts of the enterolignans enterodiol and enterolactone are sometimes found in animal foods (milk products) as a result of their production by intestinal bacterial metabolism in the animals' guts, but these are exceptions.[36-39] Little has been done to investigate the effects of storage and processing on lignans in most foods,[29-32,40-45] although it is known that the lignan content is apparently not changed considerably with flaxseed[46-50] and sesame seed processing.[51-59]

Lignan intake

The lignan content of most foods is low and consumption of lignan-rich flaxseed and sesame seed is also low. However, these populations do eat many plant foods that contain small amounts of lignans and they do so often enough to raise their exposure to lignans.[60] Lignan intake does not usually exceed 1 mg per day in most Western populations. Estimates of lignan intakes vary from about 150 μg/day[61-64] (secoisolariciresinol and matairesinol) to about 1600 μg/day[65] (secoisolariciresinol, matairesinol, lariciresinol, pinoresinol, syringaresinol, medioresinol, enterolactone, enterodiol) (Table 2).[61-76] Intakes of the two most commonly measured lignans vary from 70 to 1000 μg/day for secoisolariciresinol[61,66] and 2 to 74 μg/day for matairesinol.[66,67] Methods are now available to quantify lariciresinol and pinoresinol in foods.[11,28] Lariciresinol[68,69] varies in the diet from 74 to 500 μg/day and pinoresinol[67,69] varies from 73 to 423 μg/day. Syringaresinol and medioresinol may also be measured.[28]

Total lignan intakes vary from country to country because of different dietary sources, but they vary even more depending on variations in the completeness of the food composition tables used, other methodological differences, and on how many individual lignans were analyzed and reported by investigators. More recent studies tend to have more complete analyses.[60] Valsta et al's 2003 study[70] measuring only matairesinol and secoisolariciresinol found the mean total lignan intake of Finns to be 434 μg/day. Milder et al's 2005 study[71] of lariciresinol, matairesinol, pinoresinol, and secoisolariciresinol found median total lignan intake of the Dutch was 979 μg/day. Hedelin et al's 2008 study[65] including lariciresinol, matairesinol, medioresinol, pinoresinol, secoisolariciresinol and syringaresinol of Swedish women had a median total lignan intake of 1632 μg/day. These studies indicate that, as expected, when more lignans are measured and quantified in foods, total lignan intakes increase. This challenges the interpretation of studies, particularly of meta-analyses, on lignans and health because it is difficult to compare the intakes that were reported. Muir et al[17] and Li et al[16] discuss these issues in greater depth using examples from their work on secoisolariciresinol in flaxseed, its diglucoside and its oligomer.

Lignan metabolism

Absorption of plant lignans and bioconversion of plant lignans to enterolignans and their subsequent absorption varies greatly from person to person. Lignans are present in plants both as aglycones (without sugars) and as glycosides (with sugars).[12] At present, only in flaxseed has secoisolariciresinol been found as a lignan oligomer. Lignan glycosides are absorbed in the gastrointestinal tract after metabolism by intestinal bacteria to lignan aglycones and the enterolignans (enterolactone and enterodiol), which are formed from them. The extent of hydrolysis to release the lignans from the sugars (and in flax from the oligomer), the formation of enterolignans, and the bioavailability of these compounds vary

quite significantly from person to person. Due to these differences in metabolism in the gastrointestinal tract, lignan intake is an imperfect measure of tissue exposure.[77,78]

Bacterial metabolism in the gut

Lignan glycosides, such as the flax secoisolariciresinol diglucoside ester-linked complex[17,79] and the sesame seed sesamolin triglucoside,[14,22,80] are hydrolyzed by some of the anaerobic microbes in the gut to lignan aglycones.[80-83] The free lignans are then converted into enterolignans through a series of metabolic reactions by various gut bacteria[77,84-86] (Figure 4). The efficiency of conversion depends on many factors, and differs considerably from one individual to another. The metabolism of the lignans in the tissues is influenced by genetic factors, but as yet these are not well understood.[87-90]

The predominant plant lignan compound in foods, secoisolariciresinol diglucoside, is metabolized in the gut to secoisolariciresinol, then to the enterolignan enterodiol and finally to enterolactone, but the conversion is never 100%. The plant lignan matairesinol is metabolized directly in the gut to the enterolignan enterolactone. In an in-vitro fecal microflora metabolism system, lariciresinol was completely converted in 24 hours into the enterolignans enterolactone (46%) and enterodiol (54%) whereas other plant lignans were incompletely converted – matairesinol (62%), secoisolariciresinol diglucoside (72%), and pinoresinol diglucoside (55%). All four were metabolized to enterolactone in part, but secoisolariciresinol and pinoresinol diglucosides were converted to enterodiol (50% of the secoisolariciresinol and 32% of the pinoresinol total doses) and then in small amounts to enterolactone (21% of the secoisolariciresinol and 19% of the pinoresinol total doses).[9] Other lignans that are metabolized to enterolactone include arctigenin, 7-hydroxymatairesinol, sesamin, and syringaresinol.[9,22,77] Smeds et al[91] found cyclolariciresinol, lariciresinol and matairesinol but not secoisolariciresinol in serum samples from a Finnish population. Penalvo et al[22,92] determined the presence of cyclolariciresinol, lariciresinol, matairesinol, pinoresinol, as well as anhydrosecoisolariciresinol, 7′-hydroxymatairesinol, secoisolariciresinol, and sesamin in plasma of Finns after the ingestion of sesame seeds (50 g).

The enterolignans enterodiol and enterolactone have been detected in the blood and urine of both humans and animals, but only small amounts of the plant lignans cyclolariciresinol, lariciresinol, matairesinol, pinoresinol, secoisolariciresinol, and syringaresinol have been found in human urine.[6,93] In contrast, *lignins* are thought to be largely inert and not absorbed in the human gut due to their polymeric nature.[94-97] It is possible that they are dietary precursors of enterolignans, but the ability of gut bacteria to transform and metabolize lignins into enterolignans has yet to be demonstrated in human studies.[25] This possibility is worth pursuing since conversion of food lignins to lignans might explain the relatively high concentrations of enterolignans in biofluids compared to lignan intakes.[98]

Enterolactone is the main circulating enterolignan and therefore serum enterolactone levels and urinary enterolactone excretion are used as biomarkers for plant lignan intakes. However, these are imperfect surrogates. Differences between lignan intakes and enterolactone production may arise because of variations in the composition of the gut microflora, conversion of some lignans into other compounds, intestinal transit time, the metabolic half-life of enterolactone, the redox state of the colon, the types of lignans present in the diet, and the use of antibiotics.[77,84,99]

Systemic metabolism

Once they are formed from the parent plant lignans by gut microbiota, the enterolignans enterodiol and enterolactone are absorbed through the colonic barrier,[100] and most are

conjugated to glucuronides in the tissues. They are usually detectable in the blood 8 to 10 hours after dietary intake.[77,78] In a recent study some plant lignans (anhydrosecoisolariciresinol, 7′-hydroxymatairesinol, cyclolariciresinol, lariciresinol, matairesinol, pinoresinol, secoisolariciresinol, and sesamin) were rapidly absorbed in the small intestine and appeared in the systemic circulation within an hour after the ingestion of sesame seeds.[22] The mechanisms responsible for the uptake of plant lignans in the small intestine are still unknown.[77,85] The pharmacokinetic characterization of lignans is an under-researched area that must be pursued if further insights are to be gained about the actual lignan compounds providing putative health benefits.

The enterolignans either enter enterohepatic circulation or are excreted in the urine, usually as glucuronides and sulfate esters.[100-102] Some free lignans and aliphatic or aromatic hydroxylated metabolites from hepatic metabolism may also be excreted.[77,85,102-104] One study found that the total amount of enterolactone and enterodiol detected in the urine was up to 40% of the ingested dose (0.9 mg/kg body wt, average 60-66 mg) of secoisolariciresinol diglucoside, and the majority of it was excreted within two days.[78]

The enterohepatic recirculation of secoisolariciresinol, sesame lignans and enterolignans is significant. In general, lignans permeating the gastrointestinal mucosa are likely to undergo extensive first pass metabolism by phase II enzymes, resulting in glucuronidation or sulfation, either in the mucosa and/or in the liver prior to their appearance in the systemic circulation.[100] Glucuronides and sulfates of secoisolariciresinol, enterolactone and enterodiol may undergo enterohepatic recirculation or simply be eliminated in the bile or urine.[86,105-108]

Lignan intakes, as evaluated with available food composition data and dietary records or even with biomarkers, are such imperfect estimates of exposure that they may obscure diet-disease relationships. In Horn-Ross et al's lignan food frequency questionnaire validation study[62] using only matairesinol and secoisolariciresinol, the correlations with urinary total enterodiol and enterolactone were only 0.16. In Bhakta et al's food frequency questionnaire validation study[64] the correlation of matairesinol and secoisolariciresinol “true intake” with plasma enterolactone was only 0.11. Since several other lignans are present in the diet and can be converted to enterolactone or enterodiol at varying rates, and some lignans are absorbed without conversion, such low correlations are not surprising. However, these problems do point to the need to improve dietary assessment methodology for these compounds.

Animal and cell lignan studies in cardiovascular areas

There are some animal[109-119] and a few in vitro cell[120-122] studies on food lignans in the area of cardiovascular disease. For purposes of this review, we have limited the focus to humans and only to food lignans, but the area is worth investigating further. However, caution is indicated since rodent, particularly rat, diets contain other phytoestrogens that may influence results. Several non-food lignans,[123,124] such as honokiol[125, 126] and magnolol,[127-130] have shown cardiovascular associations in animal and in vitro cell studies.

Lignans and cardiovascular disease risk factors

Randomized controlled trials

Most of the controlled trials to date have not used standardized, well-characterized products in which the lignans and other bioactive constituents are quantified. Dose-response data are often incomplete; so the appropriate lignan dose to obtain beneficial health effects is unknown. Another limitation of the epidemiological studies is that, in Western diets, usual

lignan intakes are extremely low. It is possible, given the positive results in some interventional studies with higher levels of lignan intakes, that usual intakes are below the threshold necessary to produce cardiovascular effects. Interventional studies with higher doses may provide more insight into the associations of lignans with cardiovascular disease. In addition, other components, such as unsaturated fatty acids present in intact flaxseed and sesame seed, could influence cardiovascular disease risk factors.

There are currently eight randomized controlled trials of lignan supplementation and blood pressure or other intermediate markers of cardiovascular disease risk in the literature; five using secoisolariciresinol diglucoside from flaxseed and three using sesamin from sesame seed. In addition, there is a recently published comprehensive meta-analysis[131] of the associations of flaxseed interventions, which included the five studies of flaxseed lignans on cardiovascular disease risk.

The population assessed may have a significant bearing on the outcomes of the lignan intervention. It is important to note that some studies were of healthy volunteers, which may show few associations with risk factors, while others were of individuals at risk.

Blood pressure studies—As shown in Table 3,[122,132-134] in a randomized double blind placebo-controlled trial of lignan supplementation in ninety-two healthy older individuals with a walking program, a daily dose of 543 mg secoisolariciresinol diglucoside (187 mg secoisolariciresinol) plus exercise for six months significantly reduced diastolic blood pressure (-2 mm Hg) in middle-aged hypertensive Canadian men (n=42) but did not in women (n=50), and had no association with systolic blood pressure.[132] In a Chinese study of seventy-three type 2 diabetics of the same age range who were fed 360 mg secoisolariciresinol diglucoside (124 mg secoisolariciresinol) per day for twelve weeks no significant associations with systolic or diastolic blood pressure were observed at this dose.[133]

However, in a Japanese double blind crossover placebo controlled study, 60 mg sesamin (in 180 mg wheat germ oil) per day for four weeks significantly reduced both diastolic (-1.9 mm Hg) and systolic (-3.9 mm Hg) blood pressure in mildly hypertensive middle-aged men (n=23) and women (n=2).[134] But among thirty-three overweight Australian men and women with one or more risk factors for metabolic syndrome, fed ~50 mg per day of sesame lignans in a five week randomized controlled crossover study to determine if the sesame supplement reduced 20-hydroxyeicosatetraenoic acid (20-HETE) (a metabolite of arachidonic acid and a proposed prohypertensive agent in humans), neither systolic nor diastolic blood pressure were lowered. However, the sesame lignan supplementation decreased both plasma and urine 20-HETE significantly, suggesting that lignans may have other cardiovascular disease risk modulating activity.[122]

Lipoprotein studies—As shown in Table 4,[131-133, 135-139] in the Chinese study of seventy-three diabetics who were fed 360 mg secoisolariciresinol diglucoside (124 mg secoisolariciresinol) per day for twelve weeks, no associations with lipid profiles, fasting glucose levels or vascular sensitivity were evident although glycemic control was improved.[133] When twenty-two healthy Danish postmenopausal women were fed 500 mg secoisolariciresinol diglucoside (172 mg of secoisolariciresinol) per day for six weeks, secoisolariciresinol did not have any significant association with total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) or triglycerides.[135]

In the Canadian study of secoisolariciresinol supplementation (approximately 187 secoisolariciresinol as 543 mg secoisolariciresinol diglucoside per day) and a walking

program of ninety-two healthy middle aged adults for twenty-six weeks, HDL, LDL, total cholesterol, triglycerides and the metabolic syndrome composite score were not significantly affected by lignan supplementation.[132] However, the administration of secoisolariciresinol diglucoside 600 mg per day (approximately 206 mg secoisolariciresinol) in a Chinese randomized double blind placebo controlled trial[136] of fifty-five hypercholesterolemic adults significantly reduced total and LDL over eight weeks. Triglycerides were reduced but not significantly and HDL was not affected. When eleven perimenopausal United States (US) women with mild hyperlipidemia took 200 mg secoisolariciresinol diglucoside per day (approximately 69 mg secoisolariciresinol) for fourteen weeks, LDL, total cholesterol and lipoprotein (a) were reduced.[137] When all these data[132,133,135-137] were pooled in a meta-analysis,[131] total and LDL were significantly reduced, although type of intervention, sex and initial lipid values affected the observed associations. The authors concluded that the association of flaxseed or lignan interventions on blood lipids subjects was suggestive but remained unclear and required further evaluation.[131]

Other cardiovascular risk factors—As shown in Table 5,[132,137,139-141] In a randomized placebo controlled Japanese trial,[138] 65 mg per day of sesamin significantly reduced total and LDL and apolipoprotein B in twelve hypercholesterolemic adults over eight weeks although HDL and triglycerides were not affected. However, Wu et al's Australian study[139] of thirty-three overweight adults using ~50 mg per day sesamin (39.5 mg sesamin and 12.2 mg sesamolin in 26.2 g sesame seeds) for five weeks had no association with any lipids or C-reactive protein but did lower F_2-isoprostanes. It is possible that doses were too low, the study duration was too short, or the other compounds in the sesame seeds such as fatty acids obscured potential positive associations.

Five hundred mg secoisolariciresinol diglucoside (172 mg secoisolariciresinol) per day for six weeks blunted a rise in C-reactive protein in twenty-two Danish women, which was evident in controls.[140] Pan et al[141] found that 360 mg secoisolariciresinol diglucoside (124 mg secoisolariciresinol) per day for twelve weeks significantly decreased C-reactive protein in sixty-four type 2 diabetic patients, particularly women (n=39). Marblestone[137] found 69 mg secoisolariciresinol per day for fourteen weeks reduced C-reactive protein in eleven perimenopausal women with mild hyperlipidemia.

Overall it appears that, in sufficient doses, secoisolariciresinol and sesamin may reduce risk factors of cardiovascular disease. However, the studies to date have been mostly small and in populations with varying susceptibility. Clinical trials with flaxseed and sesame seed products have resulted in ambiguous results because little attention was paid to providing an adequate description of the test material. Without knowledge of the actual lignan content in the tested material it is difficult to ascribe outcomes to lignan administration. A major issue with many of the clinical trials (until more recently) is product quality and lack of a detailed description for the tested material. Future controlled trials should focus on target groups at high risk of cardiovascular disease. Interventions should include doses of well-characterized supplement products high enough in lignan content and have trial durations that are long enough to be expected to demonstrate beneficial associations.

Observational studies: Lignan intake

There are significant challenges in measuring lignan intakes, including the incompleteness of food tables, the failure to measure all the lignans present, the inability to account for individual differences in production of enterolignans in the gut, and the failure to use validated biomarkers of intake. Table 6 shows that the evidence for a cardiovascular benefit from dietary lignan intake in existing epidemiological studies is mixed.[66,72,75,76,142-145] We found only two studies on dietary intake of lignans and their associations with

cardiovascular disease or coronary heart disease events or mortality and five studies with heart disease risk factor endpoints. Milder et al[76] assessed lignan intakes in Dutch elderly men and followed them for cardiovascular disease mortality over 15 years. The rate ratios [and 95% confidence interval (CI)] per 1-SD (standard deviation) difference in matairesinol intake (which is metabolized directly to enterolactone) were 0.72 (0.53, 0.98) for coronary heart disease mortality and 0.83 (0.69, 1.00) for cardiovascular disease mortality. Neither total lignans nor the other lignans consumed (lariciresinol, pinoresinol, secoisolariciresinol) were related to coronary heart disease or cardiovascular disease mortality. There was also no association between lignan intakes and diastolic blood pressure, systolic blood pressure, HDL and total cholesterol.

In the Dutch EPIC cohort study[66] of women who were followed for a median of 6.25 years, lignan intakes (matairesinol and secoisolariciresinol) of approximately 1100 μg/day were not associated with CVD disease risk. However, increasing lignan intake was associated with lower CHD risk but only among smokers. Relationships with individual lignans were not reported in that study.[66]

Supporting Milder et al's findings,[76] Pellegrini et al[75] also found greater matairesinol intakes were significantly associated with increased flow mediated dilatation in older Italian men and women but no significant associations were observed with secoisolariciresinol, pinoresinol, or lariciresinol or total lignans. These findings are intriguing because, compared to the other lignans, matairesinol is found in much lower amounts (e.g., only a tenth) than other lignans in the diet.

Three observational studies examining blood pressure outcomes found negligible associations with greater lignan intake.[72,76,142] In a cross-sectional study of postmenopausal women in the US, lignan intake was associated with a borderline, non-statistically significant association with lower diastolic or systolic blood pressure.[72] In a Dutch cross-sectional study of women, although there was a trend toward lower systolic and diastolic blood pressure and a lesser prevalence of hypertension with higher intake (albeit levels of 750 μg) of two lignans (matairesinol and secoisolariciresinol), these findings were not significant.[142]

Observational studies of the relationship between lignan intake and total cholesterol and its subfractions are mixed. Two observational studies[72,143] of Dutch and US women had no significant association with LDL, HDL or total cholesterol, but a third observational study[144] of US men found that lignan intake was associated significantly with increased LDL and apolipoprotein B and nonsignificantly with increased total cholesterol. This same study found that lignan intake was significantly associated with lower C-peptide.[144] In the cross-sectional study in Framingham, Massachusetts (USA), postmenopausal women with greater intake of lignans had a lower fasting triglyceride concentration.[72]

In regard to markers of vascular function, in addition to the aforementioned study of flow mediated dilatation,[75] a Dutch study[145] found lignan intake non-significantly associated with reduced aortic stiffness in all postmenopausal women but significantly associated with reduced aortic stiffness in the subset of women 20 to 30 years beyond menopause. Kreijkamp-Kasper et al's study[142] also examined these markers in Dutch postmenopausal women but found no significant association with endothelial function, flow mediated dilatation, and ankle brachial index.

In the Milder et al prospective cohort[76] and the Pellegrini et al cross-sectional vascular[75] studies, which measured specific lignan dietary intakes, matairesinol appeared to be the lignan most commonly associated with decreased cardiovascular disease risk. However, this may have been simply because matairesinol is more commonly measured in foods compared

to the other lignans. Matairesinol occurs particularly in wine, oats and rye. Among populations consuming wine, the amount of matairesinol provided from this source could be high enough (e.g., 17-22 mg/100g white wine or 74-98 mg/100g red wine) to provide additional protection beyond the alcohol content alone, although confounding by other components of wine cannot be ruled out. Many epidemiologic studies[146] show that whole grain intake is cardioprotective. Matairesinol may be one of the important components responsible for this association. The soluble fiber content of oats is known to be cardioprotective, and the considerable matairesinol content of whole grain oats may contribute to these protective associations.

Observational studies: Serum enterolactone

Serum levels of enterolactone are somewhat better measures of systemic lignan exposure in tissues than are lignan intakes alone, although the short half-life of both metabolites requires caution in interpreting studies of a single measure of either biomarker in relation to disease outcome.[60,78] It may be useful to keep in mind that it has been suggested that levels of enterolactone above 30 nmol/l or higher are protective, and levels below 15 nmol/l are too low to confer protections. Upper levels of enterolactone from diet appear to be 90-100 nmol/l, however variations in levels are high.[147,148] Table 7 illustrates findings from four epidemiological studies that examined plasma enterolactone in relation to risk of coronary heart disease mortality, cardiovascular disease mortality and events, and other related risk factors (blood pressure, HDL and LDL).[149-153] In most of the studies in Table 7, the highest quartiles and quintiles approached or were in the putative protective range.

In a cohort study of 1889 Finnish men who were followed for an average of 12.2 years, Vanharanta et al[149] found lower risk of fatal coronary heart disease [Rate Ratio (RR) = 0.44, p=0.03] and fatal cardiovascular disease (RR 0.55, p=0.04) with greater concentrations of serum enterolactone. In contrast, associations with all-cause mortality were weaker and not significant (data not shown).[149]

In a nested case-control study of healthy Finnish men where blood levels of enterolactone was measured up to 7.7 years prior to diagnosis, those with mean serum concentrations of enterolactone in the highest quartile (>30.1 nmol/L) had a 65.3% lower risk of acute coronary events than men in lowest quartile (<7.21 nmol/L).[150] In another Finnish study among men, where blood was measured up to 11 years before diagnosis, the association between mean serum enterolactone concentration and coronary heart disease risk (acute and fatal) was not significant in cases compared to healthy controls (17.8 nmol/L vs 18.1 nmol/L) when adjusted for classic risk factors.[151] In a Dutch nested case control study of men and women, no significant differences were found between serum enterolactone levels in coronary heart disease acute events.[152]

Two Finnish nested case-control studies[149,150] of blood pressure noted significant inverse associations with plasma enterolactone, where as in a third Finnish study[151] and a Dutch study[152] associations were not statistically significant. All of the nested case control studies of cardiovascular disease and coronary heart disease outcomes found no association between enterolactone levels and blood lipids (HDL, LDL, total cholesterol, apolipoprotein B), apart from a borderline positive association in one Dutch study.[152] In a cross-sectional Finnish study, high enterolactone levels were associated with reduced F_2-isoprostanes, a marker of lipid peroxidation.[153] The weak correlations between serum enterolactone and cardiovascular disease outcomes make it difficult to draw conclusions from those studies.

Limitations of existing studies

Although many of the studies reviewed suggest possible associations with dietary or biomarker measures of lignan exposure, several limitations are worth noting. More research on the food content of lignans, and on food sources in relation to health outcomes in epidemiologic studies is needed. It may be that a certain threshold of intake is required and many Western populations either do not reach those levels, or the appropriate foods are not assessed on research questionnaires. If possible, repeated measures of these biomarkers would benefit studies of the association between enterolactone and chronic disease outcomes. Finally, it is of interest that most studies of the lignan intake were of women, whereas all but one of the enterolactone studies were of men. Because associations with lignans may vary by sex, more research including both men and women is needed. Future studies should employ both complete dietary intakes of lignans and serum (or plasma) enterolignan markers in high-risk groups.

Are lignans the components that provide cardiovascular benefits?

Can the cardioprotective benefits of foods rich in lignans be ascribed to lignans, lignins, dietary fiber, alkylresorcinols or other components? Both lignins and lignans are synthesized from similar subunits, and both, as well as other components of dietary fiber, are commonly found in cereals and grains.

Of the few studies on lignins, the various types of lignins in foods were not examined independently. One study of fiber components[154] and a recent review[155] found that lignin did not lower lipids. However, several observational studies examining lignin and cancer risk found reduced risk of colorectal[156,157] oral, pharyngeal and esophageal[158] cancers but not with breast,[159] ovarian,[160] and renal[161] cancers.

Dietary fiber may be responsible in part for associations observed with lignan intake. Dietary fiber,[162-166] particularly soluble fiber,[164,167-169] reduces risk of cardiovascular disease. Dietary fiber lowers blood pressure,[170,171] decreases C-reactive protein levels,[172-176] decreases metabolic syndrome[177-179] and decreases insulin resistance.[180] Although some studies indicate dietary fiber has weak lipid lowering associations,[181,182] soluble fiber is more highly associated with lower serum lipids,[183-188] lower blood pressure[189] and fewer symptoms of metabolic syndrome.[190,191]

Cereal fiber consists more of insoluble fibers (lignins) than soluble fibers. Cereal fiber is associated with decreased insulin resistance,[192] lower serum lipids,[193] lower blood pressure,[194,195] less progression of coronary atherosclerosis in postmenopausal women with established coronary artery disease,[196] reduced risk not only of coronary heart disease,[165,197,198] but also of cardiovascular disease[199] and stroke[200] in many[201] but not all studies.[164,202,203] Insoluble fiber is associated with lower blood pressure,[189] lower C-reactive protein levels,[176] lower insulin resistance,[180] and lower risk of both cardiovascular disease[168] and myocardial infarction.[164,168]

The studies on lignan intakes and cardiovascular disease risk, which were reviewed earlier in the article,[66,72,75,76,142-145] were adjusted for fiber intakes, but not separately for insoluble and soluble fiber. Thus, the associations with lignan intake described here were over and above those of fiber. In the four epidemiological studies using enterolactone as the marker of lignan intakes, results were mixed.[149-152] Serum enterolactone was positively correlated with fiber intake in one study[150] but fiber intake had no consistent association with the risk of acute coronary events. In a second study by the same investigator[149] energy adjusted fiber intake was associated with enterolactone and explained 6% of its variation. However, in a third study, another group of investigators[151] found that adjusting for fiber

and other dietary factors had little association with results. The fourth study also found fiber intake significantly associated with plasma enterolactone and enterodiol.[152] It is possible that enterolactone is a biomarker for a heart-healthy diet, and that such a diet exerts its effects through many different constituents (alkylresorcinols, flavonoids, glucosinolates, lignans, lignins, phenolic acids, stilbenes, terpenes, etc.).

In cereals the fiber fraction contains alkylresorcinols, folic acid, polyphenols, Vitamin E and other factors in addition to lignans, which may also be involved in cardioprotection. However, in some cohort studies the associations between lignan intake and cardiovascular disease mortality remain even after adjusting for dietary fiber intakes. Whether the associations observed with coronary heart disease and cardiovascular disease risk and lignan exposure might be explained by intakes of cereal fiber or alcohol rather than by lignan intakes themselves remains to be determined. Nevertheless, in several controlled trials that used higher lignan doses than usually found in diets, such as a secoisolariciresinol diglucoside enriched source (500 mg/day secoisolariciresinol diglucoside), there were positive associations. Since secoisolariciresinol diglucoside enriched products are available today and some cardiovascular risk reducing associations were noted with their use, there is some support for a role of lignans in cardiovascular disease risk reduction. Now that high quality products with well-characterized lignan contents are available, studies done with these well-characterized products may shed light on whether lignans do in fact have cardioprotective properties. Studies in experimental animals will also be helpful, particularly in exploring possible mechanisms of action.

Conclusion

There is intriguing but not yet compelling evidence from epidemiological studies that lignans present in the very small quantities typical of usual Western diets, decrease coronary heart disease and cardiovascular disease mortality. More research is needed to confirm or refute these associations. Intervention studies using higher doses have found positive associations with some cardiovascular risk factors. In addition, it is important to elucidate whether doses found in foods or only the larger doses that might be delivered in dietary supplements offer protection.

Acknowledgments

Funding and support. This work was supported in part with resources from the United States Department of Agriculture (USDA), Cooperative State Research, Education, and Extension Service grant #2006-35200-17259, the USDA, Agricultural Research Service, under agreement No. 58-1950-7-707, and NIH National Heart, Lung and Blood Institute grant R21HL087217. Any opinions, findings, conclusions or recommendations expressed here are those of the authors and do not necessarily reflect the view of the USDA.

References

1. Penttinen P, Jaehrling J, Damdimopoulos AE, Inzunza J, Lemmen JG, van der Saag P, Pettersson K, Gauglitz G, Makela S, Pongratz I. Diet-derived polyphenol metabolite enterolactone is a tissue-specific estrogen receptor activator. Endocrinology. 2007; 148(10):4875–86. [PubMed: 17628008]
2. Adlercreutz H. Lignans and human health. Critical Reviews in Clinical Laboratory Sciences. 2007; 44(5):483–525. [PubMed: 17943494]
3. Adlercreutz H, Mousavi Y, Clark J, Hockerstedt K, Hamalainen E, Wahala K, Makela T, Hase T. Dietary phytoestrogens and cancer: in vitro and in vivo studies. Journal of Steroid Biochemistry and Molecular Biology. 1992; 41:331–337. [PubMed: 1314077]
4. Setchell KDR, Lawson AM, Mitchell FL, Adlercreutz H, Kirk DN, Axelson M. Lignans in man and animal species. Nature. 1980; 287:740–742. [PubMed: 6253812]

5. Davin LB, Lewis NG. Dirigent proteins and dirigent sites explain the mystery of specificity of radical precursor coupling in lignan and lignin biosynthesis. Plant Physiology. 2000; 123(2):453–62. [PubMed: 10859176]
6. Raffaelli B, Hoikkala A, Leppala E, Wahala K. Enterolignans. Journal of Chromatography B Analytical Technological Biomedical Life Sciences. 2002; 777:29–43.
7. Saleem M, Kim HJ, Ali MS, Lee YS. An update on bioactive plant lignans. Natural Product Reports. 2005; 22(6):696–716. [PubMed: 16311631]
8. Umezawa T. Diversity in lignan biosynthesis. Phytochemistry Reviews. 2003; 2:371–390.
9. Heinonen S, Nurmi T, Liukkonen K, Poutanen K, Wahala K, Deyama T, Nishibe S, Adlercreutz H. In vitro metabolism of plant lignans: new precursors of mammalian lignans enterolactone and enterodiol. Journal of Agricultural and Food Chemistry. 2001; 49(7):3178–3186. [PubMed: 11453749]
10. Mazur WM, Duke JA, Wahala K, Rasku S, Adlercreutz H. Isoflavonoids and lignans in legumes: nutritional and health aspects in humans. Journal of Nutritional Biochemistry. 1998; 9(4):193–200.
11. Milder IEJ, Arts ICW, Venema DP, Lasaroms JJP, Wahala K, Hollman PCH. Optimization of a liquid chromatography-tandem mass spectrometry method for quantification of the plant lignans secoisolariciresinol, matairesinol, lariciresinol, and pinoresinol in foods. Journal of Agricultural and Food Chemistry. 2004; 52(15):4643–4651. [PubMed: 15264894]
12. Smeds AI, Eklund PC, Sjoholm RE, Willfor SM, Nishibe S, Deyama T, Holmbom BR. Quantification of a broad spectrum of lignans in cereals, oilseeds, and nuts. Journal of Agricultural and Food Chemistry. 2007; 55:1337–1346. [PubMed: 17261017]
13. Katsuzaki H, Kawakishi S, Osawa T. Sesaminol glucosides in sesame seeds. Phytochemistry. 1994; 35(3):773–776. [PubMed: 7764592]
14. Kim KS, Park SH, Choung MG. Nondestructive determination of lignans and lignan glycosides in sesame seeds by near infrared reflectance spectroscopy. Journal of Agricultural and Food Chemistry. 2006; 54(13):4544–4550. [PubMed: 16786996]
15. Ryu SN, Ho CT, Osawa T. High performance liquid chromatographic determination of antioxidant lignan glycosides in some varieties of sesame. Journal of Food Lipids. 1998; 5(1):17–28.
16. Li X, Yuan JP, Xu SP, Wang JH, Liu X. Separation and determination of secoisolariciresinol diglucoside oligomers and their hydrolysates in the flaxseed extract by high-performance liquid chromatography. Journal of Chromatography, A. 2008; 1185(2):223–232. [PubMed: 18272161]
17. Muir AD. Flax lignans - analytical methods and how they influence our understanding of biological activity. Journal of AOAC International. 2006; 89(4):1147–1157. [PubMed: 16915858]
18. Strandas C, Kamal-Eldin A, Andersson R, Aman P. Composition and properties of flaxseed phenolic oligomers. Food Chemistry. 2008; 110(1):106–112.
19. Struijs K, Vincken JP, Verhoef R, van Oostveen-van Casteren WHM, Voragen AGJ, Gruppen H. The flavonoid herbacetin diglucoside as a constituent of the lignan macromolecule from flaxseed hulls. Phytochemistry. 2007; 68(8):1227–1235. [PubMed: 17141814]
20. Struijs K, Vincken JP, Verhoef R, Voragen AGJ, Gruppen H. Hydroxycinnamic acids are ester-linked directly to glucosyl moieties within the lignan macromolecule from flaxseed hulls. Phytochemistry. 2008; 69(5):1250–1260. [PubMed: 18187168]
21. Struijs K, Vincken JP, Doeswijk TG, Voragen AGJ, Gruppen H. The chain length of lignan macromolecule from flaxseed hulls is determined by the incorporation of coumaric acid glucosides and ferulic acid glucosides. Phytochemistry. 2009; 70(2):262–269. [PubMed: 19155025]
22. Penalvo JL, Heinonen SM, Aura AM, Adlercreutz H. Dietary sesamin is converted to enterolactone in humans. Journal of Nutrition. 2005; 135(5):1056–62. [PubMed: 15867281]
23. Davin LB, Jourdes M, Patten AM, Kim KW, Vassao DG, Lewis NG. Dissection of lignin macromolecular configuration and assembly: Comparison to related biochemical processes in allyl/propenyl phenol and lignan biosynthesis. Natural Products Reports. 2008; 25:1015–90.
24. Hatfield R, Vermerris W. Lignin formation in plants. The dilemma of linkage specificity Plant Physiology. 2001; 126:1351–1357.
25. Begum A, Nicolle C, Mila I, Lapierre C, Nagano K, Fukushima K, Heinonen S, Adlercreutz H, Remesy C, Scalbert A. Dietary lignins are precursors of mammalian lignans in rats. Journal of Nutrition. 2004; 134:120–127. [PubMed: 14704303]

26. DeVries J. On defining dietary fibre. Proceedings of the Nutrition Society. 2003; 62:37–43. [PubMed: 12740055]
27. Muir, AD.; Westcott, ND., editors. Flax, The Genus Linum. London: Taylor & Francis; 2003.
28. Penalvo JL, Haajanen KM, Botting N, Adlercreutz H. Quantification of lignans in food using isotope dilution gas chromatography/mass spectrometry. Journal of Agricultural and Food Chemistry. 2005; 53(24):9342–9347. [PubMed: 16302745]
29. Kuhnle GGC, Dell'Aquila C, Aspinall SM, Runswick SA, Mulligan AA, Bingham SA. Phytoestrogen content of cereals and cereal-based foods consumed in the UK. Nutrition and Cancer. 2009; 61(3):302–309. [PubMed: 19373603]
30. Milder IE, Arts IC, van de Putte B, Venema DP, Hollman PC. Lignan contents of Dutch plant foods: a database including lariciresinol, pinoresinol, secoisolariciresinol and matairesinol. British Journal of Nutrition. 2005; 93:393–402. [PubMed: 15877880]
31. Penalvo JL, Adlercreutz H, Uehara M, Ristimaki A, Watanabe S. Lignan content of selected foods from Japan. Journal of Agricultural and Food Chemistry. 2008; 56:401–409. [PubMed: 18163563]
32. Thompson LU, Boucher BA, Zhen Liu, Cotterchio M, Kreiger N. Phytoestrogen content of foods consumed in Canada, including isoflavones, lignans, and coumestan. Nutrition and Cancer. 2006; 54(2):184–201. [PubMed: 16898863]
33. Adlercreutz H, Mazur W. Phyto-oestrogens and Western diseases. Annals of Medicine. 1997; 29(2):95–120. [PubMed: 9187225]
34. Mazur W, Fotsis T, Wahala K, Ojala S, Salakka A, Adlercreutz H. Isotope dilution gas chromatographic-mass spectrometric method for the determination of isoflavonoids, coumestrol, and lignans in food samples. Analytical Biochemistry. 1996; 233(2):169–80. [PubMed: 8789715]
35. Mazur W. Phytoestrogen content in foods. Bailliere's Clinical Endocrinology and Metabolism. 1996; 12(4):729–742.
36. Antignac JP, Cariou R, le Bizec B, Andre F. New data regarding phytoestrogens content in bovine milk. Food Chemistry. 2004; 87(2):275–281.
37. Kuhnle GGC, Dell'Aquila C, Aspinall SM, Runswick SA, Mulligan AA, Bingham SA. Phytoestrogen content of foods of animal origin: dairy products, eggs, meat, fish, and seafood. Journal of Agricultural and Food Chemistry. 2008; 56(21):10099–10104. [PubMed: 18922017]
38. Gagnon N, Cortes C, da Silva D, Kazama R, Benchaar C, dos Santos G, Zeoula L, Petit HV. Ruminal metabolism of flaxseed (Linum usitatissimum) lignans to the mammalian lignan enterolactone and its concentration in ruminal fluid, plasma, urine and milk of dairy cows. British Journal of Nutrition. 2009; 102(7):1015–23. [PubMed: 19393113]
39. Smeds AI, Willfor SM, Pietarinen SP, Peltonen-Sainio P, Reunanen MH. Occurrence of “mammalian” lignans in plant and water sources. Planta. 2007; 226(3):639–46. [PubMed: 17497165]
40. Brenes M, Garcia A, Dobarganes MC, Velasco J, Romero C. Influence of thermal treatments simulating cooking processes on the polyphenol content in virgin olive oil. Journal of Agricultural and Food Chemistry. 2002; 50(21):5962–5967. [PubMed: 12358466]
41. Kikuzaki H, Kayano S, Fukutsuka N, Aoki A, Kasamatsu K, Yamasaki Y, Mitani T, Nakatani N. Abscisic acid related compounds and lignans in prunes (*Prunus domestica* L) and their oxygen radical absorbance capacity (ORAC). Journal of Agricultural and Food Chemistry. 2004; 52(2): 344–349. [PubMed: 14733519]
42. Liukkonen KH, Katina K, Wilhelmsson A, Myllymaki O, Lampi AM, Kariluoto S, Piironen V, Heinonen SM, Nurmi T, Adlercreutz H, Peltoketo A, Pihlava JM, Hietaniemi V, Poutanen K. Process-induced changes on bioactive compounds in whole grain rye. Proceedings of the Nutrition Society. 2003; 62(1):117–122. [PubMed: 12740066]
43. Nilsson M, Aman P, Harkonen H, Hallmans G, Knudsen KEB, Mazur W, Adlercreutz H. Nutrient and lignan content, dough properties and baking performance of rye samples used in Scandinavia. Acta Agriculturae Scandinavica Section B, Soil and Plant Science. 1997; 47(1):26–34.
44. Penalvo JL, Heinonen SM, Nurmi T, Deyama T, Nishibe S, Adlercreutz H. Plant lignans in soy-based health supplements. Journal of Agricultural and Food Chemistry. 2004; 52(13):4133–4138. [PubMed: 15212459]

45. Romero C, Brenes M, Yousfi K, Garcia P, Garcia A, Garrido A. Effect of cultivar and processing method on the contents of polyphenols in table olives. Journal of Agricultural and Food Chemistry. 2004; 52(3):479–484. [PubMed: 14759136]
46. Hall CA III, Manthey FA, Lee RE, Niehaus M. Stability of alpha -linolenic acid and secoisolariciresinol diglucoside in flaxseed fortified macaroni. Journal of Food Science. 2005; 70(8):C483–C489.
47. Hyvarinen HK, Pihlava JM, Hiidenhovi JA, Hietaniemi V, Korhonen HJT, Ryhanen EL. Effect of processing and storage on the stability of flaxseed lignan added to bakery products. Journal of Agricultural and Food Chemistry. 2006; 54(1):48–53. [PubMed: 16390176]
48. Hyvarinen HK, Pihlava JM, Hiidenhovi JA, Hietaniemi V, Korhonen HJT, Ryhanen EL. Effect of processing and storage on the stability of flaxseed lignan added to dairy products. Journal of Agricultural and Food Chemistry. 2006; 54(23):8788–8792. [PubMed: 17090123]
49. Muir AD, Westcott ND. Quantitation of the lignan secoisolariciresinol diglucoside in baked goods containing flax seed or flax meal. Journal of Agricultural and Food Chemistry. 2000; 48(9):4048–4052. [PubMed: 10995312]
50. Strandas C, Kamal-Eldin A, Andersson R, Aman P. Phenolic glucosides in bread containing flaxseed. Food Chemistry. 2008; 110(4):997–999.
51. Choi SD, Cho MJ. Changes in fractionation pattern of the sesame seed lipid and minor components during storage. Journal of the Korean Agricultural Chemical Society. 1983; 26(4):255–260.
52. Kim IH, Choe EN. Effects of bleaching on the properties of roasted sesame oil. Journal of Food Science. 2005; 70(1):C48–C52.
53. Kumar CM, Rao AGA, Singh SA. Effect of infrared heating on the formation of sesamol and quality of defatted flours from *Sesamum indicum* L. Journal of Food Science. 2009; 74(4):H105–H111. [PubMed: 19490327]
54. Lee SW, Jeung MK, Park MH, Lee SY, Lee JH. Effects of roasting conditions of sesame seeds on the oxidative stability of pressed oil during thermal oxidation. Food Chemistry. 2010; 118(3):681–685.
55. Moazzami AA, Haese SL, Kamal-Eldin A. Lignan contents in sesame seeds and products. European Journal of Lipid Science and Technology. 2007; 109(10):1022–1027.
56. Shahidi F, Amarowicz R, Abou-Gharbia HA, Shehata AAY. Endogenous antioxidants and stability of sesame oil as affected by processing and storage. Journal of the American Oil Chemists' Society. 1997; 74(2):143–148.
57. Wu WH. The contents of lignans in commercial sesame oils of Taiwan and their changes during heating. Food Chemistry. 2007; 104(1):341–344.
58. Yen GC. Influence of seed roasting process on the changes in composition and quality of sesame (*S*esame *indicum*) oil. Journal of the Science of Food and Agriculture. 1990; 50(4):563–570.
59. Yoshida H, Abe S, Hirakawa Y, Takagi S. Roasting effects on fatty acid distributions of triacylglycerols and phospholipids in sesame (*Sesamum indicum*) seeds. Journal of the Science of Food and Agriculture. 2001; 81(7):620–626.
60. Webb AL, McCullough ML. Dietary lignans: potential role in cancer prevention. Nutrition and Cancer. 2005; 51(2):117–31. [PubMed: 15860433]
61. Horn-Ross PL, Hoggatt KJ, Lee MM. Phytoestrogens and thyroid cancer risk: the San Francisco Bay Area thyroid cancer study. Cancer Epidemiology, Biomarkers & Prevention. 2002; 11(1):43–9.
62. Horn-Ross PL, Barnes S, Lee VS, Collins CN, Reynolds P, Lee MM, Stewart SL, Canchola AJ, Wilson L, Jones K. Reliability and validation of an assessment of usual phytoestrogen consumption (United States). Cancer Causes & Control. 2006; 17(1):85–93. [PubMed: 16411057]
63. Tedeschi-Blok N, Lee M, Sison JD, Miike R, Wrensch M. Inverse association of antioxidant and phytoestrogen nutrient intake with adult glioma in the San Francisco Bay Area: a case-control study. BMC Cancer. 2006; 6:148. 12 pages. 10.1186/1471-2407-6-148 [PubMed: 16749939]
64. Bhakta D, dos Santos Silva I, Higgins C, Sevak L, Kassam-Khamis T, Mangtani P, Adlercreutz H, McMichael A. A semiquantitative food frequency questionnaire is a valid indicator of the usual intake of phytoestrogens by south Asian women in the UK relative to multiple 24-h dietary recalls and multiple plasma samples. Journal of Nutrition. 2005; 135(1):116–23. [PubMed: 15623842]

65. Hedelin M, Lof M, Olsson M, Adlercreutz H, Sandin S, Weiderpass E. Dietary phytoestrogens are not associated with risk of overall breast cancer but diets rich in coumestrol are inversely associated with risk of estrogen receptor and progesterone receptor negative breast tumors in Swedish women. Journal of Nutrition. 2008; 138(5):938–45. [PubMed: 18424605]
66. van der Schouw YT, Kreijkamp-Kaspers S, Peeters PH, Keinan-Boker L, Rimm EB, Grobbee DE. Prospective study on usual dietary phytoestrogen intake and cardiovascular disease risk in Western women. Circulation. 2005; 111(4):465–71. [PubMed: 15687135]
67. Galvan-Portillo MV, Wolff MS, Torres-Sanchez LE, Lopez-Cervantes M, Lopez-Carrillo L. Assessing phytochemical intake in a group of Mexican women. Salud Publica de Mexico. 2007; 49(2):126–31. [PubMed: 17522739]
68. Cotterchio M, Boucher BA, Kreiger N, Mills CA, Thompson LU. Dietary phytoestrogen intake--lignans and isoflavones--and breast cancer risk (Canada). Cancer Causes & Control. 2008; 19(3): 259–72. [PubMed: 17992574]
69. Touillaud MS, Thiebaut AC, Fournier A, Niravong M, Boutron-Ruault MC, Clavel-Chapelon F. Dietary lignan intake and postmenopausal breast cancer risk by estrogen and progesterone receptor status. Journal of the National Cancer Institute. 2007; 99(6):475–86. [PubMed: 17374837]
70. Valsta L, Kilkkinen A, Mazur W, Nurmi T, Lampi A, Ovaskainen M, Korhonen T, Adlercreutz H, Pietinen P. Phyto-oestrogen database of foods and average intake in Finland. British Journal of Nutrition. 2003; 89:S31–38. [PubMed: 12725654]
71. Milder IEJ, Feskens EJM, Arts ICW, de Mesquita HBB, Hollman PCH, Kromhout D. Intake of the plant lignans secoisolariciresinol, matairesinol, lariciresinol, and pinoresinol in Dutch men and women. Journal of Nutrition. 2005; 135(5):1202–1207. [PubMed: 15867304]
72. de Kleijn MJ, van der Schouw YT, Wilson PW, Grobbee DE, Jacques PF. Dietary intake of phytoestrogens is associated with a favorable metabolic cardiovascular risk profile in postmenopausal U. S. women: the Framingham study. Journal of Nutrition. 2002; 132(2):276–82. [PubMed: 11823590]
73. Linseisen J, Piller R, Hermann S, Chang-Claude J. German Case-control Study. Dietary phytoestrogen intake and premenopausal breast cancer risk in a German case-control study International. Journal of Cancer. 2004; 110(2):284–90.
74. Nagel G, Mack U, von Fournier D, Linseisen J. Dietary phytoestrogen intake and mammographic density -- results of a pilot study. European Journal of Medical Research. 2005; 10(9):389–94. [PubMed: 16183551]
75. Pellegrini N, Valtueña S, Ardigò D, Brighenti F, Franzini L, Del Rio D, Scazzina F, Piatti PM, Zavaroni I. Intake of the plant lignans matairesinol, secoisolariciresinol, pinoresinol, and lariciresinol in relation to vascular inflammation and endothelial dysfunction in middle age-elderly men and post-menopausal women living in Northern Italy. Nutrition, Metabolism & Cardiovascular Disease. 2010; 20(1):64–71.
76. Milder IE, Feskens EJ, Arts IC, Bueno-de-Mesquita HB, Hollman PC, Kromhout D. Intakes of 4 dietary lignans and cause-specific and all-cause mortality in the Zutphen Elderly Study. American Journal of Clinical Nutrition. 2006; 84(2):400–5. [PubMed: 16895890]
77. Clavel T, Dore J, Blaut M. Bioavailability of lignans in human subjects. Nutrition Research Reviews. 2006; 19(2):187–196. [PubMed: 19079885]
78. Kuijsten A, Arts IC, Vree TB, Hollman PC. Pharmacokinetics of enterolignans in healthy men and women consuming a single dose of secoisolariciresinol diglucoside. Journal of Nutrition. 2005; 135:795–801. [PubMed: 15795437]
79. Kuijsten A, Arts IC, van't Veer P, Hollman PC. The relative bioavailability of enterolignans in humans is enhanced by milling and crushing of flaxseed. Journal of Nutrition. 2005; 135(12): 2812–6. [PubMed: 16317125]
80. Jan KC, Hwang LS, Ho CT. Biotransformation of sesaminol triglucoside to mammalian lignans by intestinal microbiota. Journal of Agricultural & Food Chemistry. 2009; 57(14):6101–6. [PubMed: 19537732]
81. Clavel T, Henderson G, Alpert CA, Philippe C, Rigottier-Gois L, Dore J, Blaut M. Intestinal bacterial communities that produce active estrogen-like compounds enterodiol and enterolactone in humans. Applied & Environmental Microbiology. 2005; 71(10):6077–85. [PubMed: 16204524]

82. Clavel T, Henderson G, Engst W, Dore J, Blaut M. Phylogeny of human intestinal bacteria that activate the dietary lignan secoisolariciresinol diglucoside. FEMS Microbiology Ecology. 2006; 55(3):471–478. [PubMed: 16466386]
83. Yuan JP, Li X, Xu SP, Wang JH, Liu X. Hydrolysis kinetics of secoisolariciresinol diglucoside oligomers from flaxseed. Journal of Agricultural & Food Chemistry. 2008; 56(21):10041–7. [PubMed: 18925741]
84. Clavel T, Borrmann D, Braune A, Dore J, Blaut M. Occurrence and activity of human intestinal bacteria involved in the conversion of dietary lignans. Anaerobe. 2006; 12(3):140–7. [PubMed: 16765860]
85. Lampe JW, Atkinson C, Hullar MA. Assessing exposure to lignans and their metabolites in humans. Journal of AOAC International. 2006; 89(4):1174–81. [PubMed: 16915861]
86. Liu Z, Saarinen NM, Thompson LU. Sesamin is one of the major precursors of mammalian lignans in sesame seed (*Sesamum indicum*) as observed in vitro and in rats. Journal of Nutrition. 2006; 136:906–912. [PubMed: 16549449]
87. Fuchs D, Piller R, Linseisen J, Daniel H, Wenzel U. The human peripheral blood mononuclear cell proteome responds to a dietary flaxseed-intervention and proteins identified suggest a protective effect in atherosclerosis. Proteomics. 2007; 7(18):3278–88. [PubMed: 17708591]
88. Low YL, Taylor JI, Grace PB, Dowsett M, Scollen S, Dunning AM, Mulligan AA, Welch AA, Luben RN, Khaw KT, Day NE, Wareham NJ, Bingham SA. Phytoestrogen exposure correlation with plasma estradiol in postmenopausal women in European Prospective Investigation of Cancer and Nutrition-Norfolk may involve diet-gene interactions. Cancer Epidemiology, Biomarkers & Prevention. 2005; 14(1):213–20.
89. Low YL, Taylor JI, Grace PB, Dowsett M, Folkerd E, Doody D, Dunning AM, Scollen S, Mulligan AA, Welch AA, Luben RN, Khaw KT, Day NE, Wareham NJ, Bingham SA. Polymorphisms in the CYP19 gene may affect the positive correlations between serum and urine phytoestrogen metabolites and plasma androgen concentrations in men. Journal of Nutrition. 2005; 135(11):2680–6. [PubMed: 16251630]
90. Low YL, Dunning AM, Dowsett M, Folkerd E, Doody D, Taylor J, Bhaniani A, Luben R, Khaw KT, Wareham NJ, Bingham SA. Phytoestrogen exposure is associated with circulating sex hormone levels in postmenopausal women and interact with ESR1 and NR1I2 gene variants. Cancer Epidemiology, Biomarkers & Prevention. 2007; 16(5):1009–16.
91. Smeds AI, Hakala K, Hurmerinta TT, Kortela L, Saarinen NM, Makela SI. Determination of plant and enterolignans in human serum by high-performance liquid chromatography with tandem mass spectrometric detection. Journal of Pharmaceutical and Biomedical Analysis. 2006; 41(3):898–905. [PubMed: 16460900]
92. Penalvo JL, Nurmi T, Haajanen K, Al-Maharik N, Botting N, Adlercreutz H. Determination of lignans in human plasma by liquid chromatography with coulometric electrode array detection. Analytical Biochemistry. 2004; 332(2):384–393. [PubMed: 15325308]
93. Nurmi T, Voutilainen S, Nyyssonen K, Adlercreutz H, Salonen JT. Liquid chromatography method for plant and mammalian lignans in human urine. Journal of Chromatography B. 2003; 798:101–110.
94. Holloway WD, Tasman-Jones C, Lee SP. Digestion of certain fractions of dietary fiber in humans. American Journal of Clinical Nutrition. 1978; 31(6):927–30. [PubMed: 665553]
95. Joshi S, Agte V. Digestibility of dietary fiber components in vegetarian men. Plant Foods for Human Nutrition. 1995; 48(1):39–44. [PubMed: 8719737]
96. Kelsay JL, Goering HK, Behall KM, Prather ES. Effect of fiber from fruits and vegetables on metabolic responses of human subjects: fiber intakes, fecal excretions, and apparent digestibilities. American Journal of Clinical Nutrition. 1981; 34(9):1849–52. [PubMed: 6269418]
97. Van Dokkum W, Pikaar NA, Thissen JT. Physiological effects of fibre-rich types of bread. 2. Dietary fibre from bread: digestibility by the intestinal microflora and water-holding capacity in the colon of human subjects. British Journal of Nutrition. 1983; 50(1):61–74. [PubMed: 6309212]
98. Horner NK, Kristal AR, Prunty J, Skor HE, Potter JD, Lampe JW. Dietary determinants of plasma enterolactone. Cancer Epidemiology, Biomarkers & Prevention. 2002; 11(1):121–6.

99. Kilkkinen A, Stumpf K, Pietinen P, Valsta LM, Tapanainen H, Adlercreutz H. Determinants of serum enterolactone concentration. American Journal of Clinical Nutrition. 2001; 73(6):1094–100. [PubMed: 11382665]
100. Jansen GH, Arts IC, Nielen MW, Muller M, Hollman PC, Keijer J. Uptake and metabolism of enterolactone and enterodiol by human colon epithelial cells. Archives of Biochemistry & Biophysics. 2005; 435(1):74–82. [PubMed: 15680909]
101. Adlercreutz H, Vanderwildt J, Kinzel J, Attalla H, Wähälä K, Makela T, Hase T, Fotsis T. Lignan and isoflavonoid conjugates in human urine. Journal of Steroid Biochemistry and Molecular Biology. 1995; 52:97–103. [PubMed: 7857879]
102. Knust U, Hull WE, Spiegelhalder B, Bartsch H, Strowitzki T, Owen RW. Analysis of enterolignan glucuronides in serum and urine by HPLC-ESI-MS. Food & Chemical Toxicology. 2006; 44(7):1038–49. [PubMed: 16488523]
103. Jacobs E, Metzler M. Oxidative metabolism of the mammalian lignans enterolactone and enterodiol by rat, pig, and human liver microsomes. Journal of Agricultural & Food Chemistry. 1999; 47(3):1071–7. [PubMed: 10552418]
104. Niemeyer HB, Honig DM, Kulling SE, Metzler M. Studies on the metabolism of the plant lignans secoisolariciresinol and matairesinol. Journal of Agricultural & Food Chemistry. 2003; 51(21): 6317–25. [PubMed: 14518962]
105. Dean B, Chang S, Doss GA, King C, Thomas PE. Glucuronidation, oxidative metabolism, and bioactivation of enterolactone in rhesus monkeys. Archives of Biochemistry & Biophysics. 2004; 429(2):244–51. [PubMed: 15313229]
106. Jan KC, Ho CT, Hwang LS. Elimination and metabolism of sesamol, a bioactive compound in sesame oil, in rats. Molecular Nutrition & Food Research. 2009; 53(Suppl 1):S36–43. [PubMed: 19156718]
107. Jan KC, Hwang LS, Ho CT. Tissue distribution and elimination of sesaminol triglucoside and its metabolites in rat. Molecular Nutrition & Food Research. 2009; 53(7):815–25. [PubMed: 19517453]
108. Rowland I, Faughnan M, Hoey L, Wahala K, Williamson G, Cassidy A. Bioavailability of phyto-oestrogens. British Journal of Nutrition. 2003; 89(Suppl 1):S45–58. [PubMed: 12725656]
109. Ide T, Ashakumary L, Takahashi Y, Kushiro M, Fukuda N, Sugano M. Sesamin, a sesame lignan, decreases fatty acid synthesis in rat liver accompanying the down-regulation of sterol regulatory element binding protein-1. Biochimica et Biophysica Acta. 2001; 1534(1):1–13. [PubMed: 11750882]
110. Kong X, Yang JR, Guo LQ, Xiong Y, Wu XQ, Huang K, Zhou Y. Sesamin improves endothelial dysfunction in renovascular hypertensive rats fed with a high-fat, high-sucrose diet. European Journal of Pharmacology. 2009; 620(1-3):84–9. [PubMed: 19699195]
111. Matsumura Y, Kita S, Ohgushi R, Okui T. Effects of sesamin on altered vascular reactivity in aortic rings of deoxycorticosterone acetate-salt-induced hypertensive rat. Biological & Pharmaceutical Bulletin. 2000; 23(9):1041–5. [PubMed: 10993201]
112. Nakano D, Kurumazuka D, Nagai Y, Nishiyama A, Kiso Y, Matsumura Y. Dietary sesamin suppresses aortic NADPH oxidase in DOCA salt hypertensive rats. Clinical & Experimental Pharmacology & Physiology. 2008; 35(3):324–6. [PubMed: 17941888]
113. Penalvo JL, Hopia A, Adlercreutz H. Effect of sesamin on serum cholesterol and triglycerides levels in LDL receptor-deficient mice. European Journal of Nutrition. 2006; 45(8):439–44. [PubMed: 17039285]
114. Penumathsa SV, Koneru S, Zhan L, John S, Menon VP, Prasad K, Maulik N. Secoisolariciresinol diglucoside induces neovascularization-mediated cardioprotection against ischemia-reperfusion injury in hypercholesterolemic myocardium. Journal of Molecular & Cellular Cardiology. 2008; 44(1):170–9. [PubMed: 18001768]
115. Prasad K. Flaxseed and cardiovascular health. Journal of Cardiovascular Pharmacology. 2009; 54(5):369–77. [PubMed: 19568181]
116. Prasad K. Hypocholesterolemic and antiatherosclerotic effect of flax lignan complex isolated from flaxseed. Atherosclerosis. 2005; 179(2):269–75. [PubMed: 15777541]

117. Prasad K. Regression of hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinol diglucoside isolated from flaxseed. Atherosclerosis. 2008; 197(1):34–42. [PubMed: 17904562]

118. Sano T, Oda E, Yamashita T, Shiramasa H, Ijiri Y, Yamashita T, Yamamoto J. Antithrombic and anti-atherogenic effects of partially defatted flaxseed meal using a laser-induced thrombosis test in apolipoprotein E and low-density lipoprotein receptor deficient mice. Blood Coagulation & Fibrinolysis. 2003; 14(8):707–12. [PubMed: 14614348]

119. Yamashita K, Ikeda S, Obayashi M. Comparative effects of flaxseed and sesame seed on vitamin E and cholesterol levels in rats. Lipids. 2003; 38(12):1249–55. [PubMed: 14870927]

120. Cho SH, Lee HR, Kim TH, Choi SW, Lee WJ, Choi Y. Effects of defatted safflower seed extract and phenolic compounds in diet on plasma and liver lipid in ovariectomized rats fed high-cholesterol diets. Journal of Nutritional Science & Vitaminology. 2004; 50(1):32–7. [PubMed: 15228215]

121. Penumathsa SV, Koneru S, Thirunavukkarasu M, Zhan L, Prasad K, Maulik N. Secoisolariciresinol diglucoside: relevance to angiogenesis and cardioprotection against ischemia-reperfusion injury. Journal of Pharmacology & Experimental Therapeutics. 2007; 320(2):951–9. [PubMed: 17132814]

122. Wu JH, Hodgson JM, Clarke MW, Indrawan AP, Barden AE, Puddey IB, Croft KD. Inhibition of 20-hydroxyeicosatetraenoic acid synthesis using specific plant lignans: in vitro and human studies. Hypertension. 2009; 54(5):1151–8. [PubMed: 19786646]

123. Chiu PY, Leung HY, Siu AH, Poon MK, Ko KM. Schisandrin B decreases the sensitivity of mitochondria to calcium ion-induced permeability transition and protects against ischemia-reperfusion injury in rat hearts. Acta Pharmacologica Sinica. 2007; 28(10):1559–65. [PubMed: 17883940]

124. Cho SH, Rhee SJ, Choi SW, Choi Y. Effects of forsythia fruit extracts and lignan on lipid metabolism. Biofactors. 2004; 22(1-4):161–3. [PubMed: 15630274]

125. Hu H, Zhang XX, Wang YY, Chen SZ. Honokiol inhibits arterial thrombosis through endothelial cell protection and stimulation of prostacyclin. Acta Pharmacologica Sinica. 2005; 26(9):1063–8. [PubMed: 16115372]

126. Tsai SK, Huang CH, Huang SS, Hung LM, Hong CY. Antiarrhythmic effect of magnolol and honokiol during acute phase of coronary occlusion in anesthetized rats: influence of L-NAME and aspirin. Pharmacology. 1999; 59(5):227–33. [PubMed: 10529654]

127. Chen YH, Lin SJ, Chen JW, Ku HH, Chen YL. Magnolol attenuates VCAM-1 expression in vitro in TNF-alpha-treated human aortic endothelial cells and in vivo in the aorta of cholesterol-fed rabbits. British Journal of Pharmacology. 2002; 135(1):37–47. [PubMed: 11786478]

128. Chen HY, Hung YC, Lee EJ, Chen TY, Chuang IC, Wu TS. The protective efficacy of magnolol in hind limb ischemia-reperfusion injury. Phytomedicine. 2009; 16(10):976–81. [PubMed: 19577912]

129. Jin YC, Kim KJ, Kim YM, Ha YM, Kim HJ, Yun UJ, Bae KH, Kim YS, Kang SS, Seo HG, Lee JH, Chang KC. Anti-apoptotic effect of magnolol in myocardial ischemia and reperfusion injury requires extracellular signal-regulated kinase1/2 pathways in rat in vivo. Experimental Biology & Medicine. 2008; 233(10):1280–8. [PubMed: 18641058]

130. Lee YM, Hsiao G, Chen HR, Chen YC, Sheu JR, Yen MH. Magnolol reduces myocardial ischemia/reperfusion injury via neutrophil inhibition in rats. European Journal of Pharmacology. 2001; 422(1-3):159–67. [PubMed: 11430926]

131. Pan A, Yu D, Demark-Wahnefried W, Franco OH, Lin X. Meta-analysis of the effects of flaxseed interventions on blood lipids. American Journal of Clinical Nutrition. 2009; 90(2):288–97. [PubMed: 19515737]

132. Cornish SM, Chilibeck PD, Paus-Jennsen L, Biem HJ, Khozani T, Senanayake V, Vatanparast H, Little JP, Whiting SJ, Pahwa P. A randomized controlled trial of the effects of flaxseed lignan complex on metabolic syndrome composite score and bone mineral in older adults. Applied Physiology, Nutrition, & Metabolism = Physiologie Appliquee, Nutrition et Metabolisme. 2009; 34(2):89–98.

133. Pan A, Sun J, Chen Y, Ye X, Li H, Yu Z, Wang Y, Gu W, Zhang X, Chen X, Demark-Wahnefried W, Liu Y, Lin X. Effects of a flaxseed-derived lignan supplement in type 2 diabetic

patients: a randomized, double-blind, cross-over trial. PLoS One. 2007; 2:e1148. [PubMed: 17987126]

134. Miyawaki T, Aono H, Toyoda-Ono Y, Maeda H, Kiso Y, Moriyama K. Antihypertensive effects of sesamin in humans. Journal of Nutritional Science & Vitaminology. 2009; 55(1):87–91. [PubMed: 19352068]
135. Hallund J, Ravn-Haren G, Bugel S, Tholstrup T, Tetens I. A lignan complex isolated from flaxseed does not affect plasma lipid concentrations or antioxidant capacity in health postmenopausal women. Journal of Nutrition. 2006; 136:112–116. [PubMed: 16365068]
136. Zhang W, Wang X, Liu Y, Tian H, Flickinger B, Empie MW, Sun SZ. Dietary flaxseed lignan extract lowers plasma cholesterol and glucose concentrations in hypercholesterolaemic subjects. British Journal of Nutrition. 2008; 99(6):1301–9. [PubMed: 18053310]
137. Marblestone, B. The effects of flaxseed SDG on perimenopausal women with mild hyperlipidemia. San Diego, CA: University of San Diego; 2008. dissertation abstract
138. Hirata F, Fujita K, Ishikura Y, Hosoda K, Ishikawa T, Nakamura H. Hypocholesterolemic effect of sesame lignan in humans. Atherosclerosis. 1996; 122(1):135–36. [PubMed: 8724120]
139. Wu JH, Hodgson JM, Puddey IB, Belski R, Burke V, Croft KD. Sesame supplementation does not improve cardiovascular disease risk markers in overweight men and women. Nutrition Metabolism & Cardiovascular Diseases. 2009; 19(11):774–80. 2009b.
140. Hallund J, Tetens I, Bugel S, Tholstrup T, Bruun JM. The effect of a lignan complex isolated from flaxseed on inflammation markers in healthy postmenopausal women. Nutrition Metabolism & Cardiovascular Diseases. 2008; 18(7):497–502.
141. Pan A, Demark-Wahnefried W, Ye X, Yu Z, Li H, Qi Q, Sun J, Chen Y, Chen X, Liu Y, Lin X. Effects of a flaxseed-derived lignan supplement on C-reactive protein, IL-6 and retinol-binding protein 4 in type 2 diabetic patients. British Journal of Nutrition. 2009; 101:1145–49. [PubMed: 18775100]
142. Kreijkamp-Kaspers S, Kok L, Bots ML, Grobbee DE, van der Schouw YT. Dietary phytoestrogens and vascular function in postmenopausal women: a cross-sectional study. Journal of Hypertension. 2004; 22(7):1381–8. [PubMed: 15201555]
143. Kreijkamp-Kaspers S, Kok L, Bots ML, Grobbee DE, van der Schouw YT. Dietary phytoestrogens and plasma lipids in Dutch postmenopausal women; a cross-sectional study. Atherosclerosis. 2005; 178(1):95–100. [PubMed: 15585205]
144. van der Schouw YT, Sampson L, Willett WC, Rimm EB. The usual intake of lignans but not that of isoflavones may be related to cardiovascular risk factors in U.S. men. Journal of Nutrition. 2005; 135(2):260–6. [PubMed: 15671223]
145. van der Schouw YT, Pijpe A, Lebrun CE, Bots ML, Peeters PH, van Staveren WA, Lamberts SW, Grobbee DE. Higher usual dietary intake of phytoestrogens is associated with lower aortic stiffness in postmenopausal women. Arteriosclerosis, Thrombosis & Vascular Biology. 2002; 22(8):1316–22.
146. De Moura, FF. Whole grain intake and cardiovascular disease and whole grain intake and diabetes review. Bethesda, MD: Life Sciences Research Office Inc; November. 2008 79 pages
147. Pietinen P, Strumpf K, Mannisto S, Kataja V, Uusitupa M, Adlercreutz H. Serum enterolactone and risk of breast cancer: a case-control study in Eastern Finland. Cancer Epidemiology, Biomarkers & Prevention. 2001; 10:339–344.
148. Strumpf K, Pietinen P, Puska P, Adlercreutz H. Changes in serum enterolactone, genistein, and daidzein in a dietary intervention study in Finland. Cancer Epidemiology, Biomarkers & Prevention. 2000; 9:1369–1372.
149. Vanharanta M, Voutilainen S, Rissanen TH, Adlercreutz H, Salonen JT. Risk of cardiovascular disease-related and all-cause death according to serum concentrations of enterolactone: Kuopio Ischaemic Heart Disease Risk Factor Study. Archives of Internal Medicine. 2003; 163(9):1099–104. [PubMed: 12742810]
150. Vanharanta M, Voutilainen S, Lakka TA, van der Lee M, Adlercreutz H, Salonen JT. Risk of acute cardiovascular events according to serum concentrations of enterolactone: a prospective population-based case-control study. Lancet. 1999; 354(9196):2112–5. [PubMed: 10609816]

151. Kilkkinen A, Erlund I, Virtanen MJ, Alfthan G, Ariniemi K, Virtamo J. Serum enterolactone concentration and the risk of coronary heart disease in a case-cohort study of Finnish male smokers. American Journal of Epidemiology. 2006; 163(8):687–93. [PubMed: 16510545]

152. Kuijsten A, Bueno-de-Mesquita HB, Boer JM, Arts IC, Kok FJ, van't Veer P, Hollman PC. Plasma enterolignans are not associated with nonfatal myocardial infarction risk. Atherosclerosis. 2009; 203(1):145–52. [PubMed: 18687435]

153. Vanharanta M, Voutilainen S, Nurmi T, Kaikkonen J, Roberts LJ, Morrow JD, Adlercreutz H, Salonen JT. Association between low serum enterolactone and increased plasma F2-isoprostanes, a measure of lipid peroxidation. Atherosclerosis. 2002; 160(2):465–9. [PubMed: 11849672]

154. Hillman LC, Peters SG, Fisher CA, Pomare EW. The effects of the fiber components pectin, cellulose and lignin on serum cholesterol levels. American Journal of Clinical Nutrition. 1985; 42(2):207–13. [PubMed: 2992264]

155. Truswell AS. Dietary fibre and blood lipids. Current Opinion in Lipidology. 1995; 6(1):14–9. [PubMed: 7735708]

156. Levi F, Pasche C, Lucchini F, La Vecchia C. Dietary fibre and the risk of colorectal cancer. European Journal of Cancer. 2001; 37(16):2091–6. [PubMed: 11597389]

157. Negri E, Franceschi S, Parpinel M, La Vecchia C. Fiber intake and risk of colorectal cancer. Cancer Epidemiology, Biomarkers & Prevention. 1998; 7(8):667–71.

158. Soler M, Bosetti C, Franceschi S, Negri E, Zambon P, Talamini R, Conti E, La Vecchia C. Fiber intake and the risk of oral, pharyngeal and esophageal cancer. International Journal of Cancer. 2001; 91(3):283–7.

159. La Vecchia C, Ferraroni M, Franceschi S, Mezzetti M, Decarli A, Negri E. Fibers and breast cancer risk. Nutrition and Cancer. 1997; 28(3):264–9. [PubMed: 9343835]

160. Pelucchi C, La Vecchia C, Chatenoud L, Negri E, Conti E, Montella M, Calza S, Dal Maso L, Franceschi S. Dietary fibres and ovarian cancer risk. European Journal of Cancer. 2001; 37(17): 2235–9. [PubMed: 11677113]

161. Galeone C, Pelucchi C, Talamini R, Negri E, Montella M, Ramazzotti V, Zucchetto A, Dal Maso L, Franceschi S, La Vecchia C. Fibre intake and renal cell carcinoma: a case-control study from Italy. International Journal of Cancer. 2007; 121(8):1869–72.

162. Gimeno SG, Hirai AT, Harima HA, Kikuchi MY, Simony RF, de Barros N Jr, Cardoso MA, Ferreira SR, Japanese-Brazilian Diabetes Study Group. Fat and fiber consumption are associated with peripheral arterial disease in a cross-sectional study of a Japanese-Brazilian population. Circulation Journal. 2008; 72(1):44–50. [PubMed: 18159098]

163. Lupton JR, Turner ND. Dietary fiber and coronary disease: does the evidence support an association? Current Atherosclerosis Reports. 2003; 5(6):500–5. [PubMed: 14525684]

164. Negri E, La Vecchia C, Pelucchi C, Bertuzzi M, Tavani A. Fiber intake and risk of nonfatal acute myocardial infarction. European Journal of Clinical Nutrition. 2003; 57(3):464–70. [PubMed: 12627184]

165. Pereira MA, O'Reilly E, Augustsson K, Fraser GE, Goldbourt U, Heitmann BL, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Dietary fiber and risk of coronary heart disease: a pooled analysis of cohort studies. Archives of Internal Medicine. 2004; 164(4):370–6. [PubMed: 14980987]

166. Streppel MT, Ocke MC, Boshuizen HC, Kok FJ, Kromhout D. Dietary fiber intake in relation to coronary heart disease and all-cause mortality over 40 y: the Zutphen Study. American Journal of Clinical Nutrition. 2008; 88(4):1119–25. [PubMed: 18842802]

167. Bazzano LA, He J, Ogden LG, Loria CM, Whelton PK, National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Dietary fiber intake and reduced risk of coronary heart disease in US men and women: the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Archives of Internal Medicine. 2003; 163(16):1897–904. [PubMed: 12963562]

168. Liu S, Buring JE, Sesso HD, Rimm EB, Willett WC, Manson JE. A prospective study of dietary fiber intake and risk of cardiovascular disease among women. Journal of the American College of Cardiology. 2002; 39(1):49–56. [PubMed: 11755286]

169. Wu H, Dwyer KM, Fan Z, Shircore A, Fan J, Dwyer JH. Dietary fiber and progression of atherosclerosis: the Los Angeles Atherosclerosis Study. American Journal of Clinical Nutrition. 2003; 78(6):1085–91. [PubMed: 14668268]

170. He J, Whelton PK. Effect of dietary fiber and protein intake on blood pressure: a review of epidemiologic evidence. Clinical & Experimental Hypertension. 1999; 21(5-6):785–96. [PubMed: 10423101]

171. Lairon D, Bertrais S, Vincent S, Arnault N, Galan P, Boutron MC, Hercberg S, French Supplementation en Vitamines et Mineraux AntioXydants (SU.VI.MAX) Adult Cohort. Dietary fibre intake and clinical indices in the French Supplementation en Vitamines et Mineraux AntioXydants (SU.VI.MAX) adult cohort. Proceedings of the Nutrition Society. 2003; 62(1):11–5. [PubMed: 12740051]

172. Bo S, Durazzo M, Guidi S, Carello M, Sacerdote C, Silli B, Rosato R, Cassader M, Gentile L, Pagano G. Dietary magnesium and fiber intakes and inflammatory and metabolic indicators in middle-aged subjects from a population-based cohort. American Journal of Clinical Nutrition. 2006; 84(5):1062–9. [PubMed: 17093158]

173. King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. American Journal of Cardiology. 2003; 92(11):1335–9. [PubMed: 14636916]

174. King DE. Dietary fiber, inflammation, and cardiovascular disease. Molecular Nutrition & Food Research. 2005; 49(6):594–600. [PubMed: 15884088]

175. King DE, Egan BM, Woolson RF, Mainous AG 3rd, Al-Solaiman Y, Jesri A. Effect of a high-fiber diet vs a fiber-supplemented diet on C-reactive protein level. Archives of Internal Medicine. 2007; 167(5):502–6. [PubMed: 17353499]

176. Ma Y, Griffith JA, Chasan-Taber L, Olendzki BC, Jackson E, Stanek EJ 3rd, Li W, Pagoto SL, Hafner AR, Ockene IS. Association between dietary fiber and serum C-reactive protein. American Journal of Clinical Nutrition. 2006; 83(4):760–6. [PubMed: 16600925]

177. Carnethon MR, Loria CM, Hill JO, Sidney S, Savage PJ, Liu K, Coronary Artery Risk Development in Young Adults study. Risk factors for the metabolic syndrome: the Coronary Artery Risk Development in Young Adults (CARDIA) study, 1985-2001. Diabetes Care. 2004; 27(11):2707–15. [PubMed: 15505009]

178. Delzenne NM, Cani PD. A place for dietary fibre in the management of the metabolic syndrome. Current Opinion in Clinical Nutrition & Metabolic Care. 2005; 8(6):636–40. [PubMed: 16205465]

179. Galisteo M, Duarte J, Zarzuelo A. Effects of dietary fibers on disturbances clustered in the metabolic syndrome. Journal of Nutritional Biochemistry. 2008; 19(2):71–84. [PubMed: 17618108]

180. Ylonen K, Saloranta C, Kronberg-Kippila C, Groop L, Aro A, Virtanen SM, Botnia Dietary Study. Associations of dietary fiber with glucose metabolism in nondiabetic relatives of subjects with type 2 diabetes: the Botnia Dietary Study. Diabetes Care. 2003; 26(7):1979–85. [PubMed: 12832299]

181. de Castro TG, Gimeno SG, Ferreira SR, Cardoso MA, Japanese-Brazilian Diabetes Study Group. Association of dietary fiber with temporal changes in serum cholesterol in Japanese-Brazilians. Journal of Nutritional Science & Vitaminology. 2006; 52(3):205–10. [PubMed: 16967765]

182. Wu K, Bowman R, Welch AA, Luben RN, Wareham N, Khaw KT, Bingham SA. Apolipoprotein E polymorphisms, dietary fat and fibre, and serum lipids: the EPIC Norfolk study. European Heart Journal. 2007; 28(23):2930–6. [PubMed: 17982164]

183. Aller R, de Luis DA, Izaola O, La Calle F, del Olmo L, Fernandez L, Arranz T, Hernandez JM. Effect of soluble fiber intake in lipid and glucose levels in healthy subjects: a randomized clinical trial. Diabetes Research & Clinical Practice. 2004; 65(1):7–11. [PubMed: 15163472]

184. Bazzano LA. Effects of soluble dietary fiber on low-density lipoprotein cholesterol and coronary heart disease risk. Current Atherosclerosis Reports. 2008; 10(6):473–7. [PubMed: 18937894]

185. Castro IA, Barroso LP, Sinnecker P. Functional foods for coronary heart disease risk reduction: a meta-analysis using a multivariate approach. American Journal of Clinical Nutrition. 2005; 82(1):32–40. [PubMed: 16002797]

186. Fernandez ML. Soluble fiber and nondigestible carbohydrate effects on plasma lipids and cardiovascular risk. Current Opinion in Lipidology. 2001; 12(1):35–40. [PubMed: 11176201]

187. Flight I, Clifton P. Cereal grains and legumes in the prevention of coronary heart disease and stroke: a review of the literature. European Journal of Clinical Nutrition. 2006; 60(10):1145–59. [PubMed: 16670693]

188. Rideout TC, Harding SV, Jones PJ, Fan MZ. Guar gum and similar soluble fibers in the regulation of cholesterol metabolism: current understandings and future research priorities. Vascular Health & Risk Management. 2008; 4(5):1023–33. [PubMed: 19183750]

189. Lee YP, Puddey IB, Hodgson JM. Protein, fibre and blood pressure: potential benefit of legumes. Clinical & Experimental Pharmacology & Physiology. 2008; 35(4):473–6. [PubMed: 18307744]

190. Steemburgo T, Dall'Alba V, Almeida JC, Zelmanovitz T, Gross JL, de Azevedo MJ. Intake of soluble fibers has a protective role for the presence of metabolic syndrome in patients with type 2 diabetes. European Journal of Clinical Nutrition. 2009; 63(1):127–33. [PubMed: 17882139]

191. Ventura EE, Davis JN, Alexander KE, Shaibi GQ, Lee W, Byrd-Williams CE, Toledo-Corral CM, Lane CJ, Kelly LA, Weigensberg MJ, Goran MI. Dietary intake and the metabolic syndrome in overweight Latino children. Journal of the American Dietetic Association. 2008; 108(8):1355–9. [PubMed: 18656576]

192. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. Diabetes Care. 2004; 27(2):538–46. [PubMed: 14747241]

193. Newby PK, Maras J, Bakun P, Muller D, Ferrucci L, Tucker KL. Intake of whole grains, refined grains, and cereal fiber measured with 7-d diet records and associations with risk factors for chronic disease. American Journal of Clinical Nutrition. 2007; 86(6):1745–53. [PubMed: 18065595]

194. Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martinez-Gonzalez MA. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. Archives of Medical Research. 2006; 37(6):778–86. [PubMed: 16824939]

195. Lairon D, Arnault N, Bertrais S, Planells R, Clero E, Hercberg S, Boutron-Ruault MC. Dietary fiber intake and risk factors for cardiovascular disease in French adults. American Journal of Clinical Nutrition. 2005; 82(6):1185–94. [PubMed: 16332650]

196. Erkkila AT, Herrington DM, Mozaffarian D, Lichtenstein AH. Cereal fiber and whole-grain intake are associated with reduced progression of coronary-artery atherosclerosis in postmenopausal women with coronary artery disease. American Heart Journal. 2005; 150(1):94–101. [PubMed: 16084154]

197. Jensen MK, Koh-Banerjee P, Hu FB, Franz M, Sampson L, Gronbaek M, Rimm EB. Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. American Journal of Clinical Nutrition. 2004; 80(6):1492–9. [PubMed: 15585760]

198. Wolk A, Manson JE, Stampfer MJ, Colditz GA, Hu FB, Speizer FE, Hennekens CH, Willett WC. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. JAMA. 1999; 281(21):1998–2004. [PubMed: 10359388]

199. Mozaffarian D, Kumanyika SK, Lemaitre RN, Olson JL, Burke GL, Siscovick DS. Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. JAMA. 2003; 289(13):1659–66. [PubMed: 12672734]

200. Oh K, Hu FB, Cho E, Rexrode KM, Stampfer MJ, Manson JE, Liu S, Willett WC. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. American Journal of Epidemiology. 2005; 161(2):161–9. [PubMed: 15632266]

201. Truswell AS. Cereal grains and coronary heart disease. European Journal of Clinical Nutrition. 2002; 56(1):1–14. [PubMed: 11840174]

202. Burr ML. Secondary prevention of CHD in UK men: the Diet and Reinfarction Trial and its sequel. Proceedings of the Nutrition Society. 2007; 66(1):9–15. [PubMed: 17343767]

203. Ness AR, Hughes J, Elwood PC, Whitley E, Smith GD, Burr ML. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction trial (DART). European Journal of Clinical Nutrition. 2002; 56(6):512–8. [PubMed: 12032650]

Abbreviations

BMI	body mass index
BP	blood pressure
CI	confidence interval
HDL	high density lipoprotein cholesterol
HR	hazard rate ratio
LDL	low density lipoprotein cholesterol
OR	odds ratio
RR	rate ratio
SD	standard deviation
US or USA	United States of America
USDA	United States Department of Agriculture

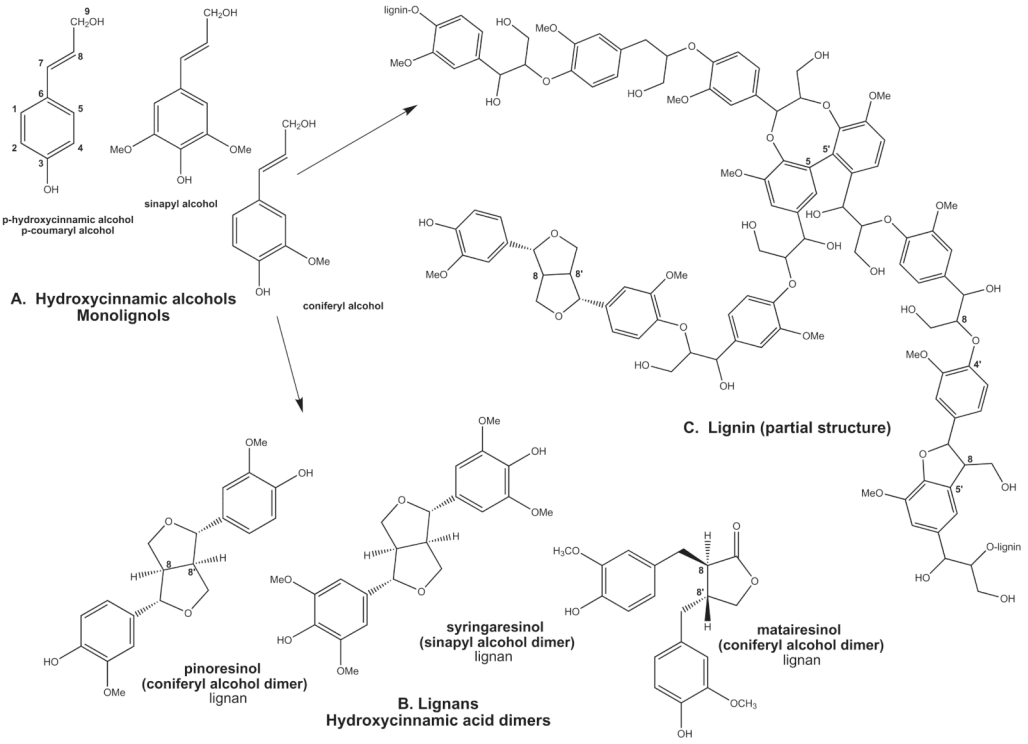

Figure 1. Structures of monolignols, lignans, and lignins

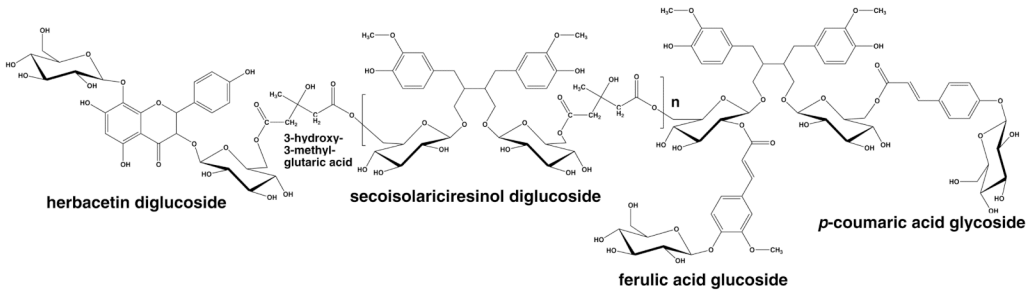

Figure 2. Sketch of flaxseed seocisolariciresinol lignan oligomer

The flavonoid herbacetin can be interchanged with secoisolariciresinol diglucoside. The number of units (n) are usually 1-7 with an average of 3. The terminal unit can have 3-hydroxy-3-methy-glutaric acid, ferulic acid glucoside or *p*-coumaric acid glucoside. Both cinnamic acid glycosides (ferulic acid glucoside or *p*-coumaric acid glucoside) are shown here to demonstrate where each one is esterified to secoisolariciresinol diglucoside. Based on work by Strandas et al (2008),[18] Struijs et al (2007),[19] Struijs et al (2008),[20] Struijs et al (2009).[21]

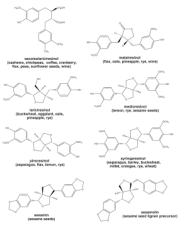

Figure 3. Structure and sources of individual lignans common in foods

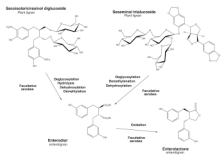

Figure 4. Bioconversion of plant lignans to enterolignans in the human gut

Simplified from and based on work by Clavel et al (2006),[84] Kuijsten et al (2005),[78] and Lampe et al (2006)[85] for secoisolariciresinol diglucoside and Jan et al (2009)[80] and Liu et al (2006)[86] for sesaminol triglucoside.

Table 1

Total µg per serving and 100 g (fresh weight) and distribution of lignans (as aglycones) in common foods and their botanical origin

common food	serving size	Total µg per serving	Total µg per 100 g	Seco	Mat	Lar	Pino	Med	Syr	Family	Genus and species
Beverages											
coffee, arabica nescafe	1 tsp	7	694	694	*					Rubiaceae	Coffea arabica
coffee, maxwell house	1 tsp	5	485	485						Rubiaceae	Coffea arabica
tea, black china brewed	8 fl oz	8	3	3	0					Theaceae	Camellia sinensis
tea, black prince of Wales brewed	8 fl oz	19	8	7	1					Theaceae	Camellia sinensis
tea, green china brewed	8 fl oz	22	9	9	1					Theaceae	Camellia sinensis
tea, green Japanese sencha brewed	8 fl oz	15	7	6	1					Theaceae	Camellia sinensis
wine, cabernet sauvignon, France, red	5 fl oz	1117	760	686	74					Vitaceae	Vitis vinifera
wine, chardonnay, France, white	5 fl oz	288	196	174	22					Vitaceae	Vitis vinifera
wine, chardonnay, Italy, white	5 fl oz	224	153	136	17					Vitaceae	Vitis vinifera
wine, chianti, reserve, Italy, red	5 fl oz	2026	1378	1280	98					Vitaceae	Vitis vinifera
Cereals											
barley whole grain	1 c	681	370	30	3	85	72	11	169	Poaceae	Hordeum vulgare
barley whole meal	1 c	75	51	51	0					Poaceae	Hordeum spp
buckwheat whole grain	1 c	1474	867	131	1	362	92	33	248	Polygonaceae	Fagopyrum esculentum
corn, whole meal	1 c	9	7	7	0					Poaceae	Zea mays
millet, common whole grain	1 c	490	245	67	3	20	85	8	62	Poaceae	Panicum miliaceum
oat whole grain	1 c	1340	859	19	71	183	194	40	352	Poaceae	Avena sativa
oat whole meal	1 c	19	12	12	0					Poaceae	Avena sativa
rice, brown	1 c	26	14	14	0					Poaceae	Oryza sativa
rye whole grain	1 c	3196	1891	38	27	324	381	148	973	Poaceae	Secale cereale
rye whole meal	1 c	128	100	42	58					Poaceae	Secale cereale
wheat whole grain	1 c	647	539	35	3	62	37	30	372	Poaceae	Triticum aestivum
wheat whole meal (emmer)	1 c	9	7	7	0					Poaceae	Triticum turgidum dicoccoides
Fruits											
apples	1 med	0	0	0	0					Rosaceae	Malus domestica
banana	1 med	3	3	3	0					Musaceae	Musa × paradisiaca

common food	serving size	Total µg per serving	Total µg per 100 g	Seco	Mat	Lar	Pino	Med	Syr	Family	Genus and species
cantaloupe	1 med wedge	12	18	18	0					Cucurbitaceae	Cucumis melo var cantalupensis
cranberry	1 c	136	136	136	0					Ericaceae	Vaccinium macrocarpon
currant, black	1 c	80	72	70	2					Grossulariaceae	Ribes nigrum
currant, red	1 c	30	27	27	0					Grossulariaceae	Ribes rubrum
grapes	10 grapes	62	126	32	0	37	28	8	21	Vitaceae	Vitis vinifera
guava	1 fruit	74	134	134	0					Myrtaceae	Psidium guajava
kiwi	1 med fruit	112	147	116	0	10	8	5	8	Actinidiaceae	Actinidia deliciosa
lemon	1 slice	23	335	4	0	25	185	64	57	Rutaceae	Citrus limon
lychee	1 fruit	1	10	10	0					Sapindaceae	Litchi chinensis
oranges	1 fruit	160	122	11	0	19	9	6	77	Rutaceae	Citrus sinensis
papaya	1 c cubes	1	1	1	0					Caricaceae	Carica papaya
pineapple	1 c chunks	284	172	7	10	67	4	3	81	Bromeliaceae	Ananas comosus
plum	1 fruit	0	1	1	0					Rosaceae	Prunus domestica
raspberry, red	10 raspberries	4	20	20	0					Rosaceae	Rubus idaeus
strawberries	1 c whole	206	143	136	7					Rosaceae	Fragaria × ananassa
Nuts, seeds, & spices											
cashews	1 oz (18 kernels)	70	247	244	4					Anacardiaceae	Anacardium occidentale
hazelnut, european hazel	1 oz (21kernels)	33	116	113	4					Betulaceae	Corylus avellana
walnuts	1 oz (14 halves)	45	160	156	5					Juglandaceae	Juglans nigra
caraway seed	1 tsp	4	204	199	5					Apiaceae	Carum carvi
cumin	1 tsp whole	4	208	203	5					Apiaceae	Cuminum cymicum
flax seed	1 tbsp	34505	335002	323670	5202	3670	2460	0	0	Linaceae	Linum usitatissimum
sesame seed^	1 tbsp	11905	132275	240	1137	14835	47136	4153	2050	Pedaliaceae	Sesamum indicum
sunflower seed	1 oz	165	581	581	0					Asteraceae	Helianthus annuus
Vegetables & legumes											
alfalfa	1 tbsp	0	2	2	0					Fabaceae	Medicago spp
asparagus	1 c	461	344	183	2	47	49	5	58	Asparagaceae	Asparagus officinalis
avocado	1 avocado	50	25	21	4					Lauraceae	Persea americana
broccoli	0. 5 c chopped	21	47	44	2					Brassicaceae	Brassica oleracea var italica
cabbage	1 c chopped	2	3	3	0					Brassicaceae	Brassica oleracea
carrot	1 medium	14	23	22	0					Apiaceae	Daucus carota subsp sativus

common food	serving size	Total µg per serving	Total µg per 100 g	Seco	Mat	Lar	Pino	Med	Syr	Family	Genus and species
cauliflower	1 c	8	8	8	0					Brassicaceae	Brassica oleracea botrytis
celery	1 c chopped	5	5	5	0					Apiaceae	Apium graveolens
chickpeas	1 tbsp	4383	35067	35067	0					Fabaceae	Cicer arietinum
chives	1 tbsp	4	117	117	0					Liliaceae	Allium schoenoprasum
cucumber	0. 5 c slices	2	4	2	0	1	1	0	0	Cucurbitaceae	Cucumis sativus
eggplant	1 c cubes	88	107	5	0	68	28	4	2	Solanaceae	Solanum melongena
garlic	1 clove	5	158	157	1					Alliaceae	Allium sativum
kidney beans	1 c	170	92	92	0					Fabaceae	Phaseolus vulgaris
lentils	1 tbsp	0	3	3	0					Fabaceae	Lens culinaris
onion	1 medium	11	10	9	1					Alliaceae	Allium cepa
peas	1 c	12114	8355	8355	0					Fabaceae	Pisum sativum
peanuts	1 c halves	401	279	279	0					Fabaceae	Arachis hypogaea
pepper	10 strips	2	8	7	0					Solanaceae	Capsicum spp
potato, sweet	1 c cubes	5	4	2	1					Convolvulaceae	Ipomea batatas
radish	0. 5 c slices	12	21	1	1	14	2	1	2	Brassicaceae	Raphanus sativus
soybeans	1 c	243	131	131	0					Fabaceae	Glycine max
tomato	1 med	26	21	1	0	11	5	2	2	Solanaceae	Lycopersicon esculentum

* blanks indicate no data available at this time for these compounds on this item

^ includes 62724 µg sesamin per 100 g sesame seed in total and per serving calculations

Abbreviations: Seco – secoisolariciresinol, Mat – matairesinol, Lar – lariciresinol, Pino – pinoresinol, Med – medioresinol, Syr – syringaresinol, all as aglycones

Data drawn from Adlercreutz & Mazur (1997),[33] Kunle et al (2009),[29] Mazur et al (1996),[34] Mazur (1998),[35] Mazur et al (1998),[10] Milder et al (2005),[30] Penalvo et al (2005),[28] Penalvo et al (2008),[31] Smeds et al (2007),[12] Thompson et al (2006)[32]

Table 2

Individual lignan intakes (μg/day) in Western countries

Location	Total	seco	mat	lar	pino	syr	med	enl	end	N	Year
USA	106	70	34							545	2002[61]
	579	534	25	*						939	2002[72]
	137	110	23							195	2006[62]
	140	115	25							846[b]	2006[63]
Canada	857	533	7	74	107					3471	2008[68]
Mexico	463[a]	123	2	237	102					50	2007[67]
	372[a]	123	2	174	73					50	2007[67]
Finland	434[a]	396	38							2862[b,e]	2003[70]
France	1112	178	11	500	423					58049	2007[69]
Germany	563	529	29							666	2004[73]
	183	167	15							7	2005[74]
	570	549	21							47	2005[74]
Italy	666	335	21	176	97					242[d]	2009[75]
Netherlands	1081	992	74							16165	2005[66]
	977	152	11	476	334					570[c]	2006[76]
	979	191	9	488	362					637[b]	2007[71]
Sweden	1632	115	24	179	149	831	322	9	0	45448	2008[65]
UK	110	101	8							108[e]	2005[64]
	149	142	9							108	2005[64]

Notes:

*blanks indicate no data

[a]means; all others are medians

[b]both men and women all others are women only, except “c”

[c] men

[d] 3 day weighed record; all others are FFQs except “e”

[e] 24 hour recall

Abbreviations: seco - secoisolariciresinol, mat - matairesinol, lar - lariciresinol, pino - pinoresinol, syr - syringaresinol, med - medioresinol, enl - enterolactone, end - enterodiol

NB: Studies that provided only combined values for matairesinol and secoisolariciresinol were not included.

Table 3

Randomized controlled trials of lignans and blood pressure

Outcome	Author, year, reference	Adult population	Vehicle	Lignan dosage per day	Study duration weeks	N	Response
Systolic	Pan et al (2007)[133]	M, F, China, type 2 diabetics, age 50-70, LDL ≥2.9 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	-0.4 mmHg p = 0.268
	Cornish et al (2009)[132]	M Canada, ≥50 years, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	42	No effect
	Cornish et al (2009)[132]	F Canada, ≥50 years, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	50	No effect
	Wu et al (2009)[122]	M, F, Australia, overweight (BMI 25-35), ≥ risk factor metabolic syndrome* or LDL > 3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5, sesamolin 12.2	5	33	-0.7 mmHg p = 0.835
	Miyawaki et al (2009)[134]	M, F, Japan, middle aged, mild hypertensives	Capsule 180 g wheat germ oil	Sesamin 60 mg	4	25	-3.5 mmHg p =0.044
Diastolic	Pan et al (2007)[133]	M, F, China, type 2 diabetics, age 50-70, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	-1.5 mmHg p = 0.751
	Cornish et al (2009)[132]	M Canada, ≥50 years, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	42	-2 mmHg p = 0.046
	Cornish et al (2009)[132]	F Canada, ≥50 years, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	50	No effect
	Wu et al (2009)[122]	M, F, Australia, overweight (BMI 25-35), ≥ 1 risk factor metabolic syndrome or LDL > 3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5, sesamolin 12.2	5	33	0.3 mmHg p = 0.223
	Miyawaki et al (2009)[134]	M, F, Japan, middle aged, mild hypertensives	Capsule 180 g wheat germ oil	Sesamin 60 mg	4	25	-1.9 mmHg p =0.045
20-HETE, plasma	Wu et al (2009)[122]	M, F, Australia, overweight (BMI 25-35), ≥ 1 risk factor metabolic syndrome or LDL > 3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5, sesamolin 12.2	5	33	-236 pmol/mmol p = 0.001
20-HETE, urine / creatinine	Wu et al (2009)[122]	M, F, Australia, overweight (BMI 25-35), ≥ 1 risk factor metabolic syndrome or LDL > 3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5, sesamolin 12.2	5	33	-47 pmol/L p = 0.001

*Metabolic syndrome composite score based on fasting glucose, HDL, triglycerides, abdominal adiposity, blood pressure, and inflammatory cytokines

Abbreviations: M – males, F – females, BMI – body mass index, BP – blood pressure, LDL – low density lipoprotein cholesterol, Seco – Secoisolariciresinol, SDG - Secoisolariciresinol diglucoside

Table 4

Randomized controlled trials of lignans and lipoproteins

Outcome	Author, year, reference	Adult population	Vehicle	Lignan dosage per day	Study duration weeks	N	Response
HDL	Pan et al (2007)[133]	M, F, China, type 2 diabetics, age 50-70, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	-0.77 mg/dl p = 0.243
	Zhang et al (2008)[136]	M, W, China, LDL ≥ 3.62 mmol/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 103 mg (300 mg SDG)	8	18	-3.86 mg/dl p < 0.001 from baseline
	Hallund et al (2006)[135]	F, Denmark, postmenopausal age 61 ± 7, healthy, BP<160/90	Muffin with flaxseed lignan complex	Seco 172 mg (500 mg SDG)	6	22	-1.54 mg/dl p = 0.531
	Zhang et al (2008)[136]	M, W, China, LDL ≥ 3.62 mmol/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 206 mg (600 mg SDG)	8	55	-5.4 mg/dl p = 0.167
	Wu et al (2009b)[139]	M, F, Australia, overweight (BMI 25-35), ≥ 1 risk factor metabolic syndrome* or LDL > 3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5, sesamolin 12.2	5	33	0.00 mg/dl p = 0.764
	Hirata et al (1996)[138]	M, Japan, hypercholesterolemic	Capsule 180 g wheat germ oil	Sesamin 32.4 mg 4 weeks then 64.8 mg 4 weeks	8	12	No effect
LDL	Pan et al (2007)[133]	M, F, China, type 2 diabetics, age 50-70, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	-4.25 mg/dl p = 0.404
	Zhang et al (2008)[136]	M, W, China, LDL ≥ 3.62 mmol/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 103 mg (300 mg SDG)	8	18	-28.6 mg/dl p < 0.001 from baseline
	Hallund et al (2006)[135]	F, Denmark, postmenopausal age 61 ± 7, healthy, BP<160/90	Muffin with flaxseed lignan complex	Seco 172 mg (500 mg SDG)	6	22	-7.72 mg/dl p = 0.184
	Cornish et al (2009)[132]	M, F Canada, ≥50 years, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	92	No effect
	Zhang et al (2008)[136]	M, W, China, LDL ≥ 3.62 mmol/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 206 mg (600 mg SDG)	8	55	-38.6 mg/dl p = 0.003

Outcome	Author, year, reference	Adult population	Vehicle	Lignan dosage per day	Study duration weeks	N	Response
	Marblestone 2008[137]	F, USA, perimenopausal, age 36-48	Flaxseed source by Brevail	Seco 69 mg (200 mg SDG)	14	11	reduced
	Pan et al (2009)[131]	Meta-analysis, 7 comparisons		Flaxseed lignan supplements			-6.18 mg/dl p = 0.03
	Wu et al (2009b)[139]	M, F, Australia, overweight (BMI 25-35), ≥ 1 risk factor metabolic syndrome or LDL > 3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5, sesamolin 12.2	5	33	2.70 mg/dl p = 0.292
	Hirata et al (1996)[138]	M, Japan, hypercholesterolemic	Capsule 180 g wheat germ oil	Sesamin 32.4 mg 4 weeks then 64.8 mg 4 weeks	8	12	-30.7 mg/dl p <0.05
Total cholesterol	Pan et al (2007)[133]	M, F, China, type 2 diabetics, age 50-70, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	-6.56 mg/dl p = 0.367
	Zhang et al (2008)[136]	M, W, China, LDL ≥ 3.62 mmol/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 103 mg (300 mg SDG)	8	18	-39.8 mg/dl p <0.001 from baseline
	Hallund et al (2006)[135]	F, Denmark, postmenopausal age 61 ± 7, healthy, BP<160/90	Muffin with flaxseed lignan complex	Seco 172 mg (500 mg SDG)	6	22	-8.88 mg/dl p = 0.262
	Cornish et al (2009)[132]	M, F Canada, ≥50 years, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	92	No effect
	Zhang et al (2008)[136]	M, W, China, LDL ≥ 3.62 mmol/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 206 mg (600 mg SDG)	8	55	-68.3 mg/dl p <0.001
	Pan et al (2009)[131]	Meta-analysis, 7 comparisons		Flaxseed lignan supplements			-10.81 mg/dl p = 0.04
	Wu et al (2009b)[139]	M, F, Australia, overweight (BMI 25-35), ≥ 1 risk factor metabolic syndrome or LDL > 3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5, sesamolin 12.2	5	33	0.77 mg/dl p = 0.227
	Hirata et al (1996)[138]	M, Japan, hypercholesterolemic	Capsule 180 g wheat germ oil	Sesamin 32.4 mg 4 weeks then 64.8 mg 4 weeks	8	12	-23.7 mg/dl p <0.05
Triglycerides	Pan et al (2007)[133]	M, F, China, type 2 diabetics, age 50-70, LDL ≥2.90 mmol/L	Capsule flaxseed lignan complex	Seco 124 mg (360 mg SDG)	12	73	-17.70 mg/dl p = 0.720

Outcome	Author, year, reference	Adult population	Vehicle	Lignan dosage per day	Study duration weeks	N	Response
	Zhang et al (2008)[136]	M, W, China, LDL ≥ 3.62 mmol/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 103 mg (300 mg SDG)	8	18	-46.0 mg/dl not significant from baseline
	Hallund et al (2006)[135]	F, Denmark, postmenopausal age 61 ± 7, healthy, BP<160/90	Muffin with flaxseed lignan complex	Seco 172 mg (500 mg SDG)	6	22	3.5 mg/dl p = 0.595
	Cornish et al (2009)[132]	M Canada, ≥50 years, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	49	Group effect (controls increased p = 0.017)
	Cornish et al (2009)[132]	F Canada, ≥50 years, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	52	No effect
	Zhang et al (2008)[136]	M, W, China, LDL ≥ 3.62 mmol/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 206 mg (600 mg SDG)	8	55	-76.1 mg/dl p = 0.068
	Wu et al (2009b)[139]	M, F, Australia, overweight (BMI 25-35), ≥ 1 risk factor metabolic syndrome or LDL > 3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5, sesamolin 12.2	5	33	-10.6 mg/dl p = 0.254
	Hirata et al (1996)[138]	M, Japan, hypercholesterolemic	Capsule 180 g wheat germ oil	Sesamin 32.4 mg 4 weeks then 64.8 mg 4 weeks	8	12	No effect
Apo A1	Pan et al (2007)[133]	M, F, China, type 2 diabetics, age 50-70, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	-2.5 mg/dl p = 0.751
Apo B	Pan et al (2007)[133]	M, F, China, type 2 diabetics, age 50-70, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	-1.6 mg/dl p = 0.528
	Hirata et al (1996)[138]	M, Japan, hypercholesterolemic	Capsule 180 g wheat germ oil	Sesamin 64.8 mg	8	12	-20.3 mg/dl p <0.05
Lp(a)	Pan et al (2007)[133]	M, F, China, type 2 diabetics, age 50-70, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	62	-2.52 mg/dl p = 0.339
	Marblestone 2008[137]	F, USA, perimenopausal, age 36-48	Flaxseed source by Brevail	Seco 69 mg (200 mg SDG)	14	11	reduced

* Metabolic syndrome composite score based on fasting glucose, HDL, triglycerides, abdominal adiposity, blood pressure, and inflammatory cytokines

Abbreviations: Apo A1 – Apolipoprotein A1, Apo B – Apolipoprotein B, Lp(a) – Lipoprotein (a), M– males, F – females, BMI – body mass index, BP – blood pressure, LDL – low density lipoprotein cholesterol, Seco – Secoisolariciresinol, SDG - Secoisolariciresinol diglucoside

Table 5

Randomized controlled trials of lignans and other cardiovascular risk factors

Outcome	Author, year, reference	Adult population	Vehicle	Lignan dosage per day	Study duration weeks	N	Response
C-reactive protein	Pan et al (2009)[141]	M, F, China, type 2 diabetics, age 50-70, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	64	-0.45 mg/l p = 0.021
	Pan et al (2009)[141]	F, China, type 2 diabetics, age 50-70, postmenopausal, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	39	-0.67 mg/l p = 0.016
	Pan et al (2009)[141]	M, China, type 2 diabetics, age 50-70, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	25	-0.20 mg/l p = 0.49
	Hallund et al (2008)[140]	F, Denmark, postmenopausal age 61 ± 7, healthy, BP<160/90	Muffin with flaxseed lignan complex	Seco 172 mg (500 mg SDG)	6	22	-0.18 mg/l p = 0.028
	Marblestone 2008[137]	F, USA, perimenopausal, age 36-48	Flaxseed source by Brevail	Seco 69 mg (200 mg SDG)	14	11	reduced
	Wu et al (2009b)[139]	M, F, Australia, overweight (BMI 25-35), ≥ 1 risk factor metabolic syndrome* or LDL > 3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5, sesamolin 12.2	5	33	-0.11mg/l p = 0.845
F_2-isoprostanes	Wu et al (2009b)[139]	M, F, Australia, overweight (BMI 25-35), ≥ 1 risk factor metabolic syndrome or LDL > 3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5, sesamolin 12.2	5	33	-35 pmol/l p = 0.047
Metabolic syndrome composite score[d]	Cornish et al (2009)[132]	M Canada, ≥50 years, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	39	0.34 (controls 0.81, p = 0.058)
	Cornish et al (2009)[132]	F Canada, ≥50 years, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	53	No effect

Abbreviations: M – males, F – females, BMI – body mass index, BP – blood pressure, LDL – low density lipoprotein cholesterol, Seco – Secoisolariciresinol, SDG - Secoisolariciresinol diglucoside

* Metabolic syndrome composite score based on fasting glucose, HDL, triglycerides, abdominal adiposity, blood pressure, and inflammatory cytokines

Table 6

Associations between matairesinol and secoisolariciresinol lignan intakes and cardiovascular disease risk and risk factors

Outcome	Author, year, reference	Study	Population characteristics	Cases (N)	p ≤0.05	p >0.05 – 0.15	p > 0.15
Cardiovascular disease mortality [b]	Milder et al (2006)[76]	Prospective cohort, Zutphen, Netherlands	570 M, elderly, 15 yr follow up	84	Mat only[a] 0.83 RR (0.69, 1.00) CI p=0.05 [7 μg per SD unit][d]		Seco only 0.88 RR (0.71, 1.08) p = 0.23 [51 μg per SD unit][d]
Coronary heart disease mortality [b]	Milder et al (2006)[76]	Prospective cohort, Zutphen, Netherlands	M, elderly, 15 yr follow up	570	Mat only 0.72 RR (0.53, 0.98) CI p=0.03 [7 μg per SD unit][d]		Seco only 0.84 RR (0.61, 1.17) p = 0.31 [51 μg per SD unit][d]
Cardiovascular disease incidence	Van der Schouw et al (2005)[66]	Prospective, EPIC, Netherlands	16,165 F, age 49-70 healthy, 6.25 yr follow up	518			0.89 HR (0.66, 1.19) CI NS [1.39 vs 0.74 mg/d][e,f]
Coronary heart disease Incidence	Van der Schouw et al (2005)[66]	Prospective, EPIC, Netherlands	16,165 F, age 49-70 healthy, 6.25 yr follow up	371			0.92 HR (0.65, 1.29) CI NS [1.39 vs 0.74 mg/d][e,f]
	Van der Schouw et al (2005)[66]	Prospective, EPIC, Netherlands	16,165 F, age 49-70 healthy, 6.25 yr follow up sub analysis by smoking status	n/a	0.63 HR (0.41, 0.98) CI p for interaction = 0.01 [1.39 vs 0.74 mg/d][e,f] smokers		No association for non-smokers
Cerebrovascular disease incidence	Van der Schouw et al (2005)[66]	Prospective, EPIC, Netherlands	16,165 F, age 49-70 healthy, 6.25 yr follow up	147			0.80 HR (0.45, 1.42) CI NS [1.39 vs 0.74 mg/d][e,f]
Hypertension	Kreijkamp-Kaspers et al (2004)[142]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60-75, healthy	301		0.49 OR (0.18, 1.29) CI	

Outcome	Author, year, reference	Study	Population characteristics	Cases (N)	p ≤0.05	p >0.05 – 0.15	p > 0.15
						p=0.15 [2.01 vs 1.14 mg/d][d,f]	
Blood pressure, diastolic	Kreijkamp-Kaspers et al (2004)[142]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60-75, healthy	301		-5.19 mm Hg (-11.41, 1.03) CI p=0.07 [2.01 vs 1.14 mg/d][d,f]	
	De Kleijn et al (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939			-1.1 mg Hg (-3.2, 1.0) CI p for trend = 0.24 [0.79 vs 0.41 mg/d][e,f]
b	Milder et al (2006)[76]	Prospective cohort, Zutphen, Netherlands	M, elderly, 15 yr follow up	570			No difference across tertiles of consumption p = 0.77
Blood pressure, systolic	Kreijkamp-Kaspers et al (2004)[142]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60-75, healthy	301		-7.92 OR (-17.91, 2.07) CI p=0.12 [2.01 vs 1.14 mg/d][d,f]	
	De Kleijn et al (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939			-2.0 mmHg (-5.8, 1.9) CI p for trend = 0.59 [0.79 vs 0.41 mg/d][e,f]
b	Milder et al (2006)[76]	Prospective cohort, Zutphen, Netherlands	M, elderly, 15 yr follow up	570			No difference across tertiles of consumption p = 0.47
Cholesterol, HDL	De Kleijn et al (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939		-2.7 mg/dl (-0.39, 5.02) CI p=0.15	

Outcome	Author, year, reference	Study	Population characteristics	Cases (N)	p ≤0.05	p >0.05 – 0.15	p > 0.15
						[0.79 vs 0.41 mg/d][e,f]	
	Kreijkamp-Kaspers et al (2005)[143]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60-75, healthy	301			0.39 mg/dl (-8.8, 6.6) CI p for trend = 0.76 [2.01 vs 1.14 mg/d][d,f]
b	Milder et al (2006)[76]	Prospective cohort, Zutphen, Netherlands	M, elderly, 15 yr follow up	570			No difference across tertiles of consumption p = 0.26
Cholesterol, LDL	Van der Schouw et al (2005)[144]	Cross-sectional, Health Professionals, USA	M, age 47-83	301	12.9 mg/dl (1.7, 24.1) CI p for trend = 0.01 [1.15 vs 0.39 mg/d medians][e,f]		
	De Kleijn et al (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939			-0.37 mg/dl (-7.3, 6.6) CI p for trend = 0.84 [0.79 vs 0.41 mg/d][e,f]
	Kreijkamp-Kaspers et al (2005)[143]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60-75, healthy	301			-8.11 mg/dl (-25.1, 8.9) CI p for trend = 0.35 [2.01 vs 1.14 mg/d][d,f]
Cholesterol, total	Van der Schouw et al (2005)[144]	Cross-sectional, Health Professionals, USA	M, age 47-83	468		11.1 mg/dl (-2.4, 24.5) CI p for trend = 0.08 [1.15 vs 0.39 mg/d medians][e,f]	
	De Kleijn et al (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939			-2.32 mg/dl (-9.6, 5.0) CI p for trend = 0.47

Outcome	Author, year, reference	Study	Population characteristics	Cases (N)	p ≤0.05	p >0.05 – 0.15	p > 0.15
							[0.79 vs 0.41 mg/d][e,f]
	Kreijkamp-Kaspers et al (2005)[143]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60-75, healthy	301			-8.11 mg/dl (-26.6, 10.4) CI p for trend = 0.40 [2.01 vs 1.14 mg/d][d,f]
b	Milder et al (2006)[76]	Prospective cohort, Zutphen, Netherlands	M, elderly, 15 yr follow up	570			No difference across tertiles of consumption p = 0.52
Triglycerides	De Kleijn et al (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939	-20.4 mg/dl (-32.7, -7.96) CI p=0.001 [0.79 vs 0.41 mg/ d][e,f]		
	Kreijkamp-Kaspers et al (2005)[143]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60-75, healthy	301			-2.65 mg/dl (-12.4, 11.5) CI p for trend = 0.78 [2.01 vs 1.14 mg/d][d,f]
Apolipoprotein B	Van der Schouw et al (2005)[144]	Cross-sectional, Health Professionals, USA	M, age 47-83	468	10.0 mg/dl (1.6, 18.4) CI p for trend = 0.02 [1.15 vs 0.39 mg/d medians][e,f]		
Lipoprotein (a)	Kreijkamp-Kaspers et al (2005)[143]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60-75, healthy	301			0.47 OR (0.17, 1.31) CI p for trend = 0.18 [2.01 vs 1.14 mg/d][d,f]
C-peptide	Van der Schouw et al (2005)[144]	Cross-sectional, Health Professionals, USA	M, age 47-83	468	-0.55 ng/dl (-0.97, -0.13) CI		

Outcome	Author, year, reference	Study	Population characteristics	Cases (N)	p ≤0.05	p >0.05 – 0.15	p > 0.15
					p for trend = 0.01 [1.15 vs 0.39 mg/d medians][e,f]		
Ankle brachial index	Kreijkamp-Kaspers et al (2004)[142]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60-75, healthy	301			0.01 (-0.04, 0.07 p for trend = 0.60 [2.01 vs 1.14 mg/d][d,f]
Endothelial function (pimax)	Kreijkamp-Kaspers et al (2004)[142]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60-75, healthy	301			-0.01 pimax (-0.08, 0.06 p for trend = 0.80 [2.01 vs 1.14 mg/d][d,f]
Flow mediated dilatation[c]	Pellegrini et al (2010)[75]	Cross-sectional, longitudinal follow-up Italy	242 M, F, healthy, postmenopausal	101	Mat only 4.1% to 8.1% change p for trend = 0.016 [0.039 vs 0.009 mg/d means][e]	Seco only 4.6% to 6.8% change p for trend = 0.099 [0.625 vs 0.158 mg/d means][e]	
	Kreijkamp-Kaspers et al (2004)[142]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60-75, healthy	301			-0.09 % (-1.93, 2.12) CI p for trend = 0.92 [2.01 vs 1.14 mg/d][d,f]
Reduced aortic stiffness	Van der Schouw et al (2002)[145]	Cross-sectional, EPIC, Netherlands	F, healthy, postmenopausal	403		-0.41 (-0.93, 0.11) CI p for trend = 0.06 [0.87 vs 0.33 mg/d][e,f]	
	Van der Schouw et al (2002)[145]	Cross-sectional, EPIC, Netherlands	F, healthy, long (20-30 years) postmenopausal time span	180	-0.80 (-1.54, -0.05) CI p for trend = 0.03		

Outcome	Author, year, reference	Study	Population characteristics	Cases (N)	p ≤0.05	p >0.05 – 0.15	p > 0.15
					[0.87 vs 0.33 mg/d][e,f]		
	Van der Schouw et al (2002)[145]	Cross-sectional, EPIC, Netherlands	F, healthy, short (8-12 years) postmenopausal time span	199			-0.19 (-0.95, 0.57) CI p for trend = 0.40 [0.87 vs 0.33 mg/d][e,f]
Metabolic syndrome score	De Kleijn et al (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939	-0.55 (-0.82, -0.28) CI p=0.0001 [0.79 vs 0.41 mg/d][e,f]		
Waist hip ratio	De Kleijn et al (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939	-0.017 (-0.030, -0.0016) CI p=0.03 [0.79 vs 0.41 mg/d][e,f]		

[a] All intakes “Mat & Seco” unless marked “Mat only” or “Seco only”

[b] not significant for lariciresinol, pinoresinol, and total lignans (secoisolariciresinol, matairesinol, lariciresinol, pinoresinol) in Milder et al (2006)[76]

[c] Flow mediated dilatation was not significant for lariciresinol and pinoresinol, but approached significance for total lignans (secoisolariciresinol, matairesinol, lariciresinol, pinoresinol) 4.7% to 7.5%, p for trend = 0.066, 666 μg/d median intake in Pellegrini et al (2009)[75]

[d] Highest versus lowest tertile of intake

[e] Highest versus lowest quartile of intake

[f] Intake from FFQ but food items scored for Mat and Seco, analytical values were not used.

Abbreviations: M – males, F – females, CI – 95% Confidence interval, HR – Hazard rate ratio, OR – Odds ratio, RR – Rate ratio, [ ] – definition of comparison groups or per SD unit, Seco – Secoisolariciresinol, Mat – matairesinol

Underlying causes of death coded according to the International Classification of Diseases, 9th and 10th revisions (ICD-9 and ICD-10). Cardiovascular disease deaths defined as ICD-9 codes 390-459 and ICD-10 codes I20-I99, coronary heart disease deaths as ICD-9 codes 410-414 (ischemic heart disease) and 492.2 (atherosclerotic heart disease) and ICD-10 codes I20-I25, and stroke as ICD-9 codes 430-438 (ischemic and hemorrhagic cerebrovascular disease) and ICD-10 codes I60-I69 (cerebrovascular diseases).

Table 7

Serum and plasma enterolactone (and enterodiol) and cardiovascular disease risk

Outcome	Author, year, reference	Study	Population characteristics	Cases (N)	p ≤0.05	p >0.05 – 0.15	p > 0.15
Cardiovascular disease mortality	Vanharanta et al (2003)[149]	Prospective, Kuopio, Finland	1889 M, age 42, 48, 54, or 60, 12.2 yr follow up	103	0.55 RR (0.29, 1.01) CI p=0.04 [23.9 vs 6.9 nmol/l][a]		
Coronary heart disease mortality	Vanharanta et al (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60, 12.2 yr follow up	70	0.44 RR (0.20, 0.96) CI p=0.03 [23.9 vs 6.9 nmol/l][a]		
	Kilkkinen et al (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 yr follow up	340 cases (205 MI, 135 deaths) 420 controls			0.57 RR (0.26, 1.25) CI p for trend=0.18 [28.25 vs 5.02 nmol/l][b]
Coronary heart disease risk (acute events & mortality)	Kilkkinen et al (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 yr follow up	340 cases (205 MI, 135 deaths) 420 controls		0.63 RR (0.33, 1.11) CI p for trend=0.07 [28.25 vs 5.02 nmol/l][b]	
Coronary heart disease risk (acute events)	Kilkkinen et al (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 yr follow up	340 cases (205 MI, 135 deaths) 420 controls		0.67 RR (0.37, 1.23) CI p for trend=0.10 [28.25 vs 5.02 nmol/l][b]	
c	Kuijsten et al (2009)[152]	Prospective nested case control Netherlands	M, F, age 20-59, 11 yr follow up	236 cases, 283 controls		1.51 OR (0.87, 2.61) CI p for trend = 0.12	

Outcome	Author, year, reference	Study	Population characteristics	Cases (N)	p ≤0.05	p >0.05 – 0.15	p > 0.15
						[17.5 vs 3.8 nmol/l][a]	
c	Kuijsten et al (2009)[152]	Prospective nested case control Netherlands	F, premenopausal, age 20-59, 11 yr follow up	34 cases	0.16 OR (0.02, 1.03) CI p for trend = 0.05 [per 13.7 nmol/l, 17.5 vs 3.8 nmol/l][a]		
c	Kuijsten et al (2009)[152]	Prospective nested case control Netherlands	F, postmenopausal, age 20-59, 11 yr follow up	30 cases	1.17 OR END (1.00, 1.36) CI p for trend = 0.05 [per 1.3 nmol/l, 1.7 vs 0.4 nmol/l][a]		2.27 OR (0.57, 8.95) CI p for trend = 0.24 [per 13.7 nmol/l, 17.5 vs 3.8 nmol/l][a]
	Vanharanta et al (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60, 7.7 yr follow up	167 cases, 167 controls	0.35 OR (0.14, 0.88) CI p=0.03 [30.1 vs 7.2 nmol/l][a]		
Hypertension	Vanharanta et al (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60, 12.2 yr follow up	1889 at baseline	-12 % p for heterogeneity <001 [23.9 vs 6.9 nmol/l][a]		
Blood pressure, diastolic	Vanharanta et al (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60, 7.7 yr follow up	167 cases, 167 controls at baseline	-3 mm Hg p for heterogeneity =0.017 [30.1 vs 7.2 nmol/l][a]		
	Vanharanta et al (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60, 12.2 yr follow up	1889 at baseline	-3 mm Hg p for heterogeneity <001 [23.9 vs 6.9 nmol/l][a]		

Outcome	Author, year, reference	Study	Population characteristics	Cases (N)	p ≤0.05	p >0.05 – 0.15	p > 0.15
c	Kuijsten et al (2009)[152]	Prospective nested case control Netherlands	M, F, age 20-59, 11 yr follow up	283 controls at baseline		-3 mm Hg p for trend = 0.08 [17.5 vs 3.8 nmol/l][a]	
	Kilkkinen et al (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 yr follow up	420 controls at baseline			-6 mm Hg p for heterogeneity = 0.21 [28.25 vs 5.02 nmol/l][b]
Blood pressure, systolic	Vanharanta et al (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60, 12.2 yr follow up	1889 at baseline	-5 mm Hg p for heterogeneity <001 [23.9 vs 6.9 nmol/l][a]		
	Vanharanta et al (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60, 7.7 yr follow up	167 cases, 167 controls at baseline	-5 mm Hg p for heterogeneity =0.026 [30.1 vs 7.2 nmol/l][a]		
c	Kuijsten et al (2009)[152]	Prospective nested case control Netherlands	M, F, age 20-59, 11 yr follow up	283 controls at baseline		-4 mm Hg p for trend = 0.09 [17.5 vs 3.8 nmol/l][a]	
	Kilkkinen et al (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 yr follow up	420 controls at baseline			-6 mm Hg p for heterogeneity = 0.84 [28.25 vs 5.02 nmol/l][b]
Cholesterol, HDL	Kuijsten[c] et al (2009)[152]	Prospective nested case control Netherlands	M, F, age 20-59, 11 yr follow up	283 controls at baseline		3.86 mg/dl p for trend = 0.07 [17.5 vs 3.8 nmol/l][a]	
	Vanharanta et al (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60, 7.7 yr follow up	167 cases, 167 controls at baseline			1.54 mg/dl p for heterogeneity = 0.74

Outcome	Author, year, reference	Study	Population characteristics	Cases (N)	p ≤0.05	p >0.05 – 0.15	p > 0.15
							[30.1 vs 7.2 nmol/l][a]
	Vanharanta et al (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60, 12.2 yr follow up	1889 at baseline			1 mg/dl p for heterogeneity = 0.66 [23.9 vs 6.9 nmol/l][a]
	Kilkkinen et al (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 yr follow up	420 controls at baseline			1.16 mg/dl p for heterogeneity = 0.47 [28.25 vs 5.02 nmol/l][b]
Cholesterol, LDL	Vanharanta et al (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60, 7.7 yr follow up	167 cases, 167 controls at baseline			-2.32 mg/dl p for heterogeneity = 0.52 [30.1 vs 7.2 nmol/l][a]
	Vanharanta et al (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60, 12.2 yr follow up	1889 at baseline			0.0 mg/dl p for heterogeneity = 0.91 [23.9 vs 6.9 nmol/l][a]
Cholesterol, total	Kuijsten [c] et al (2009)[152]	Prospective nested case control Netherlands	M, F, age 20-59, 11 yr follow up	283 controls at baseline			5.80 mg/dl p for trend = 0.22 [17.5 vs 3.8 nmol/l][a]
	Vanharanta et al (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60, 7.7 yr follow up	167 cases, 167 controls at baseline			3.47 mg/dl p for heterogeneity = 0.82 [30.1 vs 7.2 nmol/l][a]
	Kilkkinen et al (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 yr follow up	420 controls at baseline			3.86 mg/dl p for heterogeneity = 0.22 [28.25 vs 5.02 nmol/l][b]

Outcome	Author, year, reference	Study	Population characteristics	Cases (N)	p ≤0.05	p >0.05 – 0.15	p > 0.15
Apolipoprotein B	Vanharanta et al (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60, 7.7 yr follow up	167 cases, 167 controls at baseline			41 mg/l p for heterogeneity = 0.22 [30.1 vs 7.2 nmol/l][a]
Reduced F2-isoprostanes	Vanharanta et al (2002)[153]	Cross-sectional, ASAP, Finland	M, age 58.6 ± 6.5	100	-37.4% p for trend = 0.008 [25.6 vs 3.9 nmol/l][b]		

[a] Highest versus lowest quartile of serum (or plasma) enterolactone (or enterodiol

[b] Highest versus lowest quintile of serum (or plasma) enterolactone

[c] In Kuijsten et al (2009)[152] (the only study using plasma), diastolic and systolic blood pressure, HDL, total cholesterol and coronary heart disease risk (acute events) were not significant for enterodiol

Abbreviations: M – males, F – females, CI – 95% Confidence Interval, OR – Odds ratio, RR – Rate ratio, [ ] – definition of comparison groups or per SD (standard deviation) unit, END – enterodiol, MI – myocardial infarction

Underlying causes of death coded according to the International Classification of Diseases, 9th and 10th revisions (ICD-9 and ICD-10). Cardiovascular disease deaths defined as ICD-9 codes 390-459 and ICD-10 codes I20-I99, coronary heart disease deaths as ICD-9 codes 410-414 (ischemic heart disease) and 492.2 (atherosclerotic heart disease) and ICD-10 codes I20-I25, and stroke as ICD-9 codes 430-438 (ischemic and hemorrhagic cerebrovascular disease) and ICD-10 codes I60-I69 (cerebrovascular diseases).