Chapter 4

Backgrounder on Lignans

Phytoestrogens are plant chemicals that can have estrogen-like actions in humans and animals. The main phytoestrogens are isoflavones, coumestans, flavonoids and lignans (139). Lignans are widely distributed in the plant kingdom, play a role in plant growth and act as antioxidants in human metabolism. In fact, the main lignan in flax and the forms derived from it are all antioxidants. The lignans are related to lignins, which are structural elements in plants (see Chapter 1) (140). This chapter reviews the metabolism and general effects of flax lignans. The effects of lignans on cancer are described in Chapter 6.

Phytoestrogens and Sex Hormones

Phytoestrogens are similar in their chemical structure to the natural and synthetic estrogens. Depending on their concentration and other factors, phytoestrogens can act like weak estrogens by binding to the estrogen receptor on cell membranes. At other times, they act as estrogen antagonists by preventing estrogens from binding to the receptors (141).

Estrogens are female sex hormones. The main estrogens are estradiol and estrone. Testosterone is a male sex hormone. The estrogens and testosterone are steroid hormones made from cholesterol by the sex organs and to a lesser extent by the adrenal gland. The sex hormones can be found in both men and women, although men produce considerably more testosterone than estrogens, whereas women produce more estrogens than testosterone. The estrogens and testosterone are responsible for the development of adult sexual characteristics and may influence cancer processes.

Dietary phytoestrogens and human estrogens interact in many complex ways that are not well understood. Nonetheless, because phytoestrogens are biologically active, there is interest in understanding how they may help maintain health and prevent chronic diseases (139,142).

Flax Lignans

Flax is one of the richest sources of plant lignans, being very rich in the lignan secoisolariciresinol diglucoside (SDG). Flax contains other lignans as well – namely, matairesinol, pinoresinol, lariciresinol, isolariciresinol and secoisolariciresinol (often abbreviated Seco or SECO) (143,144).

Metabolism of lignans

The lignans SDG, SECO, pinoresinol, lariciresinol and matairesinol in flax are converted by bacteria in the colon to the mammalian lignans, enterodiol and enterolactone. [The flax lignan isolariciresinol is not converted to mammalian lignans (145).] Enterodiol and enterolactone are called mammalian lignans or enterolignans because they are produced in the gut of humans and other mammals; they are not found in plants. A simplified diagram showing the conversion of flax lignans to mammalian lignans is given in **Figure 4**. Enterodiol can be converted to enterolactone (146).

The biologic activity of flax and other plant lignans depends on the presence of certain bacteria in the gut (146). Some humans appear to lack either the right type or a sufficient number of gut bacteria to convert SDG and other lignans to mammalian lignans (147), and taking antibiotics virtually stops the production of enterodiol and enterolactone in the gut for several weeks (140).

Enterodiol and enterolactone have three metabolic fates: 1) They can be excreted directly in the feces; 2) They can be taken up by epithelial cells lining the human colon, conjugated with glucuronic acid or sulfate and excreted in the feces or enter the circulation (148); or 3) They can be absorbed from the gut and transported to the liver, where free forms are conjugated before being released into the bloodstream (140). Eventually, they undergo enterohepatic circulation – that is, they are secreted into bile and reabsorbed from the intestine – and are excreted in the urine in conjugated form (149). Based on a kinetic study involving 12 healthy adults, the mammalian lignans appear to be absorbed from

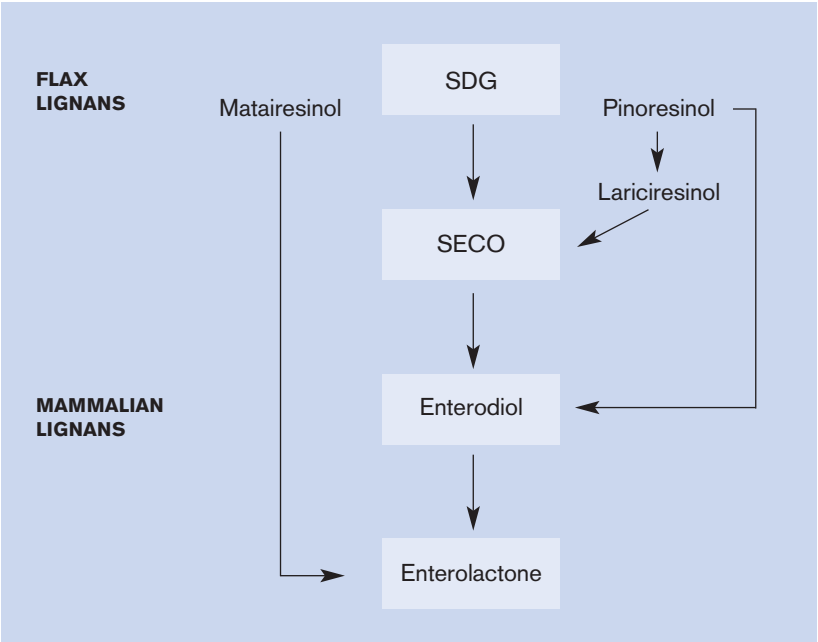
the colon about 8-10 hours after the plant lignans are eaten and reach a maximum concentration in the bloodstream about 7-10 hours later (150).

The concentration of enterodiol and enterolactone in the feces, blood and urine is related to the concentration of plants lignans in the diet – large intakes of plant lignans result in large amounts of these mammalian lignans in biological fluids. Eating flax or flax-containing food products increases the blood levels of mammalian lignans (151-154) and the excretion of mammalian lignans and/or total lignans in feces (155) and urine (151,152,154,156-159). Consuming a diet supplemented with a lignan/SDG complex derived from flax also increases mammalian lignan excretion in urine (160). The bioavailability of the mammalian lignans can be enhanced by crushing and milling flax (161).

Lignan metabolism is far more complex than originally thought. Plant lignans are not metabolized completely to mammalian lignans, and some

FIGURE 4

Metabolism of flax lignans by bacteria in the gut[a,b]



[a]Abbreviations = SDG, secoisolariciresinol diglucoside; SECO, secoisolariciresinol.
[b]Source: Adapted from Clavel (146).

plant lignans such as SECO can be detected in plasma. Furthermore, lignan metabolism may not stop at enterodiol and enterolactone, there being additional metabolites derived from these mammalian lignans. These new findings raise questions about which lignan is the most important and most biologically active form (38).

Lignan content of flax

Table 12 shows the lignan content of flax, based on figures given in two recent papers. In one paper the SDG content of flax was reported (38). The other paper reported individual flax lignans, not including SDG, and calculated the total lignan content of flax (144).

Where flax is concerned, the problem of measuring its lignan content is compounded by the structure of the seed. SDG is the major flax lignan. It does not exist in the free form in the seed; rather, it exists as a complex composed of five SDG molecules bound together with other molecules in the outer fibre layer of the seed (38,140,145). Extracting SDG from flax is difficult, and its incomplete extraction is responsible for some of the variation in SDG values reported in the literature. Some researchers have analyzed the SDG content of flax or estimated its SDG content based on the concentrations of its metabolites (e.g., SECO), as summarized by Muir (38). Other researchers, such as Thompson and coworkers (144), analyzed flax samples to quantify the content of individual lignans, including SECO, which is a key end-product of SDG metabolism (see **Figure 4**). Theoretically, the amount of SECO in flax samples reflects the amount of SDG present, provided the conversion is complete and the concentrations of pinoresinol and lariciresinol have been quantified.

Whole flax seed contains 1-26 mg SDG/g, which works out to about 11-286 mg SDG/tbsp of whole seed or about 8-208 mg SDG/tbsp of milled flax (38). Whole flax seed contains about 42 mg of total lignans/tbsp, and milled flax contains about 30 mg of total lignans/tbsp, based on an analysis of four lignans in flax: matairesinol, pinoresinol, lariciresinol and SECO (144).

Flax oil containing added lignans has been available for several years. One such product contained 0.1% SDG or about 14 mg SDG/tbsp flax oil. The amount of SDG obtained from lignan-enriched oil depends on how well the SDG particles mix with the oil. Adding SDG to flax oil is a bit like mixing oil and water – because SDG is not soluble in oil, it resists mixing with the oil and tends to settle in the bottom of the container (162).

TABLE 12

Lignan content of flax[a]

Serving Size	Lignan					
	Summarized by Muir (2006)[b]	Analyzed by Thompson et al. (2006)[c]				
	SDG	MAT	LAR	PINO	SECO	Total Lignans[d]
100 g	82-2600 mg	0.15 mg	2.8 mg	0.7 mg	375 mg	379 mg
One tbsp of whole seed (11 g)	11-286 mg	0.02 mg	0.3 mg	0.1 mg	41 mg	42 mg
One tbsp of milled flax (8 g)	8-208 mg	0.01 mg	0.2 mg	0.1 mg	30 mg	30 mg

[a] Abbreviations = LAR, lariciresinol; MAT, matairesinol; PINO, pinoresinol; SDG, secoisolariciresinol diglucoside; SECO, secoisolariciresinol.
[b] Source: Muir (38).
[c] Source: Thompson LU, et al. (144).
[d] The values for total lignans in this column were calculated by summing the values for MAT, LAR, PINO and SECO.

Flax Lignan Content Compared with Other Foods

Flax is one of the richest sources of lignans identified to date, as shown in **Table 13**. Gram for gram, flax has 47 times the total lignan content of sesame seeds and more than 600 times the total lignan content of garlic (144). Lignans are found in most fibre-rich plants: oilseeds like flax and sesame seeds; nuts; cereals; breads made with flax and/or grains; legumes and soy products; vegetables; and dried fruits (143,144).

TABLE 13

Lignan content of various foods[a]

Food group/food	Total lignans μg/g
Seeds and nuts	
Flax seeds	3790.0
Sesame seeds	80.0
Sunflower seeds	2.1
Pistachios	2.0
Chestnuts	1.9
Cereals and grains	
Flax bread	72.4
Multigrain bread	47.9
Rye bread	1.4
Legumes	
Hummus	9.8
Soy beans	2.7
Vegetables	
Garlic	5.8
Olive oil	1.4
Winter squash	1.1
Dried fruits	
Dried apricots	4.0
Dried dates	3.2
Dried prunes	1.8

[a] Source: Adapted from Thompson LU, et al. (144).

How Mammalian Lignans Work

The mammalian lignans are believed to work by binding to estrogen receptors on cell membranes, much like the body's own steroid estrogens do. The bound mammalian lignans affect the receptors' actions within the cell and ultimately the response of tissues like those of the reproductive tract. Other phytoestrogens work in the same way.

The mammalian lignans are not as powerful as the body's own estrogens, which are called endogenous estrogens. Even so, they can act as either weak estrogens or they can oppose the actions of estrogen, depending on the presence of stronger estrogens like estradiol (163). During women's reproductive years, when blood levels of endogenous estrogens are at their highest, the lignans can bind to the estrogen receptor and block the actions of endogenous estrogens. In this case, they act as antagonists. After menopause, the levels of endogenous estrogens in the blood decrease naturally because the ovaries release less natural estrogens. In this case, the lignans act like weak estrogens (163).

Biologic Effects of Lignans

Flax lignans and the mammalian lignans (enterodiol and enterolactone) are biologically active. Lignans have anticancer and antiviral effects, influence gene expression (activation) and may protect against estrogen-related diseases such as osteoporosis (139-141). Diets high in lignans may help maintain good cognitive function in post-menopausal women (164); reduce the risk of uterine fibroids in middle-aged women (165); reduce breast cancer risk in women (166); and reduce the risk of acute fatal coronary events (167) and prostate cancer (168) in men. Specific actions of lignans include the following:

- The main flax lignan SDG is an antioxidant. It scavenges for certain free radicals like the hydroxyl ion (•OH) (169). Our bodies produce free radicals continually as we use (oxidize) fats, proteins, alcohol and some carbohydrates for energy. Free radicals can damage tissues and have been implicated in the pathology of many diseases like atherosclerosis, cancer and Alzheimer disease (170). In a rat study, feeding flax at levels of 5% and 10% in the diet prior to administering a liver toxin protected against oxidative stress in liver tissue compared

with a normal diet not containing flax (171). The mammalian lignans, enterodiol and enterolactone, also act as antioxidants (172). Indeed, the antioxidant action of SECO and enterodiol is greater than that of vitamin E (173).

- The mammalian lignans affect receptors found on the surface of cell membranes. For instance, they activate the pregnane X receptor, which is involved in the metabolism of bile acids, steroid hormones and many drugs. Enterolactone is a moderate activator of the receptor, suggesting it has the ability to affect the metabolism of some drugs (174). A study conducted in France suggested that some plant lignans, along with enterodiol and enterolactone, affect hormone receptors in breast tissue. Among 58,049 French women who did not eat soy regularly, a high dietary intake of lignans (>1395 µg/day) was associated with a reduced risk of breast cancer. The benefit was limited to women with estrogen receptor positive (ER+) and progesterone receptor positive (PR+) tumours, suggesting that the biologic effects of lignans derive in part from their effects on cell hormone receptors (166).
- The mammalian lignans stimulate the synthesis of sex hormone-binding globulin (SHBG) (175), which binds sex hormones and reduces their circulation in the bloodstream, thus decreasing their biologic activity. In a meta-analysis, higher blood levels of SHBG were associated with an 80% lower risk of type 2 diabetes in women and a 52% lower risk in men (176). Low blood levels of SHBG have been found in postmenopausal women with breast cancer (177).
- The mammalian lignans inhibit the activity of aromatase, an enzyme involved in the production of estrogens (178). Decreased aromatase activity may be one way in which lignans protect against breast cancer (179).

Flax and Hormone Metabolism

Dietary fibre and fat affect estrogen levels in the body. Specifically, the intake of total fat and saturated fat is positively correlated with plasma concentrations of estradiol and estrone, whereas the intake of dietary fibre is negatively correlated with plasma levels of these hormones (180). Because flax contains both fat and dietary fibre, some researchers have investigated its effects on hormone metabolism, as described below.

Women

Flax has hormonal effects in women. In 18 premenopausal women with normal menstrual cycles, eating 10 g of flax daily for 3 months lengthened the luteal phase of the women's menstrual cycle (181). In 25 postmenopausal women who ate 25 g of milled flax daily for 2 weeks, vaginal cell maturation was stimulated, suggesting an estrogenic effect of flax on women's reproductive tract (182). However, several clinical studies lasting 2-12 weeks reported no effect of consuming 10-40 g (1+ to 5 tbsp) of milled flax daily on blood levels of estradiol, estrone, follicle-stimulating hormone or luteinizing hormone in young women of reproductive age (181) or in postmenopausal women (156,182-185). The effect of flax on menopause symptoms is discussed in Chapter 7.

Men

Flax consumption does not appear to affect sex hormone metabolism in men, based on findings of the one study published in this area. Eating 13.5 g milled flax daily for 6 weeks had no effect on plasma concentrations of testosterone, free testosterone or sex-hormone-binding globulin in six healthy young men. It is not known whether sex hormone metabolism in men is affected by long-term flax consumption (186).