# Lignans in Diets

# 36

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**Abstract**

Lignans are a large group of natural products consisting of dimers of phenyl propane units. They are found in diverse forms distributed in a variety of plants. Owing to their biological activities ranging from antioxidant, antitumor, anti-estrogenic, antivirus, anti-inflammatory to antiviral properties, they have been used for a long time both in ethnic and in conventional medicine. In particular, it may prevent hormone-dependent diseases, such as breast cancer, prostate cancer, and benign prostatic hyperplasia. However, many important scientific problems have not been constrained. This chapter has systematically reviewed the bioactive constituent, classification, distribution, bioavailability, metabolism, bioactivities, human health, application, and safety aspects of lignans. And lastly, a prospective of future studies on lignans is elucidated.

**Keywords**

Lignan · Bioactivity · Bioavailability · Metabolism · Human health

## 36.1 Introduction

Lignans are a family of secondary metabolites widely distributed in plants and human food sources. The term lignan was coined by Haworth in 1936 to describe a group of phenylpropanoid dimers in which C6-C3 units are linked by the central carbon of their propyl side chains (Stasevich et al. 2009). These compounds show dimeric structures formed by a β, β′-linkage between two phenyl propane units with a different degree of oxidation in the side chain and a different substitution pattern in the aromatic moieties. Similar to the ecological functions of several other secondary metabolites, lignans represent a means of protection against herbivores and microorganisms for the plants that synthesize them. For nomenclature purposes, the C6-C3 unit is treated as propylbenzene and numbered from 1 to 6 in the ring, starting from the propyl group, and with the propyl group numbered from 7 to 9, starting from the benzene ring. With the second C6-C3 unit, the numbers are primed. When the two C6-C3 units are linked by a bond between positions 8 and 8′, the compound is named as a "lignan" (Teponno et al. 2016).

Lignans are bioactive, non-nutrient, non-caloric, phenolic plant compounds that are found in diverse species in the plant kingdom including members of pteridophytes, gymnosperms, and angiosperms (Fuss 2003). In angiosperms, lignans have been isolated from members belonging to Asterales, Scrophulariales, Lamiales, Solanales, Apiales, Sapindales, Aristolochiales, Piperales, Laurales, Malvales, Malpighiales, and Magnoliales orders in the division Magnoliophyta (Stasevich et al. 2009). 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. It is known that lignans have remarkable ecological functions in plants, providing protection against herbivores and

microorganisms. The consumption of foods rich in lignans has potential to decrease the risk of cancers. During its long research history, this family has exhibited attractive pharmacological activities, such as antibacterial, antiviral, antitumor, antiplatelet, phosphodiesterase inhibition, 5-lipoxygenase inhibition, HIV reverse transcription inhibition, cytotoxic, antioxidant, immunosuppressive, and antiasthmatic properties (Fang and Hu 2018).

The following is an overview on the current status of research on lignans in terms of bioactive constituents, bioavailability, metabolism, bioactivities, application, toxicity, and side effects.

## 36.2 Bioactive Constituents of Lignans

Lignans are one of the largest groups of naturally occurring phenols in the plants. The lignans are derived from the shikimic acid biosynthetic pathway. Traditionally, lignans are divided into two classes: classical lignans and neolignans. It should be noted that the term lignan in the literature refers to classical lignans in most cases. Regarding the classification of classical lignans, four different types are reported. The first one arranged classical lignans into three subgroups: acyclic lignan derivatives, arylnaphthalene derivatives, and dibenzocyclooctadiene derivatives (Chang et al. 2005). The second type includes six subgroups: dibenzylbutanes, dibenzylbutyrolactones, arylnaphthalenes, dibenzocyclooctadienes, substituted tetrahydrofurans, and 2,6-diarylfurofurans (Pan et al. 2009). The third one includes seven subgroups of lignan scaffolds: cyclobutanes, tetrahydrofurans, furofurans, dibenzylbutanes, aryltetralins, cycloheptenes, and dibenzocyclooctadienes (Albertson and Lumb 2015). The fourth one is comprised of eight subgroups: furofuran, furan, dibenzylbutane, dibenzylbutyrolactone, aryltetralin, arylnaphthalene, dibenzocyclooctadiene, and dibenzylbutyrolactol (Fig. 1) (Satake et al. 2015).

In a recent review, Teponno et al. (2016) clearly described the plant source, isolation, structure, bioactivities, and synthesis of bioactive lignans. At present, 131 dibenzocyclooctadiene-type lignans have been isolated, especially from different species of *Schisandra* and *Kadsura,* such as marlignans A–L and M–S from *S. wilsoniana*; tiegusanins A–M from *S. propinqua*; neglignans A, B, and E–G, neglectalignans A–D, and neglschisandrins B, E, and F from *S. neglecta*; arisanschinins F–L from *S. arisanensis*; schilancifolignans A–C from *S. lancifolia*; kadsuphilols I–M from *Kadsura philippinensis*; and 14-*O*-demethyl polysperlignan D from *K. coccinea* (Teponno et al. 2016).

There are 16 types of lignans isolated from sesame. Most of them are fat-soluble aglycones and therefore elute into the oil on extraction. The remaining are glycosylated and have been isolated from the oil-free meal. The major aglycone lignans are sesamin and sesamolin (Dar and Arumugam 2013). Sesamol, sesaminol, sesamolinol, pinoresinol, matairesinol (MAT), lariciresinol, and episesamin form minor aglycones of sesame oil (Liu et al. 2006). The lignan glycosides include mono-, di-, and triglucosides of sesaminol, sesamolinol, and pinoresinol (Moazzami

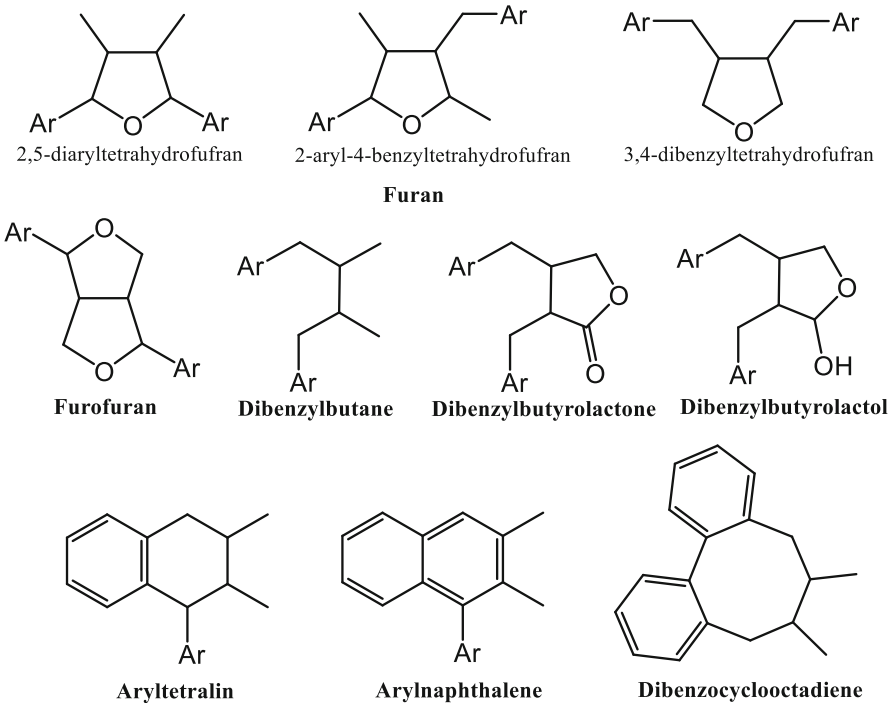


**Fig. 1** Subtypes of classical lignans (Ar = aryl)

et al. 2006). Sesaminol triglucoside, sesaminol diglucoside, and sesaminol monoglucoside are the most abundant lignan glycosides in sesame. *Sesamum alatum*, a species with winged seeds, is said to be devoid of both sesamin and sesamolin but has a novel furofuran lignan, 2-episesalatin (Kamaleldin and Yousif 1992). Three additional lignans, namely, saminol, episesaminone-9-*O*-β-D-sophoroside, and semamolactol, have been detected in the perisperm of *Sesamum indicum* (Grougnet et al. 2012). Episesaminone, a furanoketone, was characterized in part via hemisynthesis from sesamolin. Recently these authors have isolated two new lignans, namely, sesamolinol-4′-*O*-β-D-glucoside and disaminyl ether (samin dimer), from sesame seeds (Grougnet et al. 2012).

## 36.3 Bioavailability and Metabolism of Lignan

### 36.3.1 Lignan Bioavailability

A prerequisite for investigating lignan bioavailability is to accurately determine their occurrence in foods and to estimate their intake in human populations. Although flaxseed is the main source of lignans (approximately 4 mg/g dried mass), a variety of cereals, fruits, vegetables, legumes, and beverages also contain

lignans in substantial concentrations (10 ng to 400 μg/g) (Milder et al. 2005). Thus, lignans are found in a wide range of foods consumed daily in Western countries. Secoisolariciresinol diglucoside (SDG), its aglycone secoisolariciresinol (SECO), and MAT are the most frequently studied dietary lignans.

A recent study reported that the absolute oral bioavailability of schisandrin B in male and female rats was about 55.0% and 19.3%, respectively. Further, micronization technology effectively improved the bioavailability of schisandrin B (two-fold) when compared with the untreated preparation (Wang et al. 2017). Sa et al. (2015) reported that the absolute bioavailability of schisantherin A in nanoemulsion formulation was significantly enhanced from 4.3% to 47.3%. Among the various *Schisandra* lignans, schisandrol A, schisandrin B, and schisandrin C appeared to be poorly absorbed in intestinal cells. Previous studies reported that schisandrin A appears to be one of the most relatively absorbed lignans (Wang et al. 2011). In a self-emulsifying drug delivery system using oleic acid, Polysorbate 20, and Transcutol P, the bioavailability of schisandrin and schisandrin B was 292.2% and 205.8%, respectively (Shao et al. 2010).

### 36.3.2 Lignan Metabolism

Absorption of plant lignans and bioconversion of plant lignans to enterolignans and their subsequent absorption vary greatly from person to person. Lignans are present in plants both as aglycones (without sugars) and as glycosides (with sugars) (Julia et al. 2010). At present, only in flaxseed has SECO 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 (EL) and enterodiol (ED)), 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 (Clavel et al. 2006).

#### 36.3.2.1 Lignan Metabolism in the Gut

Lignans originate from cinnamic acid derivatives which are related biochemically to the metabolism of phenylalanine. Chorismic acid is transformed into prephenic acid via a Claisen rearrangement, which transfers the phosphoenolpyruvate-derived side chain so that it becomes directly bonded to the carbocycle, and thus builds up the basic carbon skeleton of phenylalanine. Decarboxylative aromatization of prephenic acid yields phenylpyruvic acid, and pyridoxal phosphate-dependent transamination leads to L-phenylalanine (Dar and Arumugam 2013). The biosynthesis of coniferyl alcohols is initiated with deamination of phenylalanine by phenylalanine ammonia lyase to form cinnamic acid, which is then hydroxylated by a P450 enzyme, cinnamate-4-hydroxylase, to form *p*-coumaric acid. Coniferyl alcohol is derived from the reduction of coumaric acid via coenzyme A ester to an aldehyde, which is further reduced in the presence of a NADPH molecule. Formation of the

coenzyme A ester facilitates the first reduction step by introducing a better leaving group ($CoAS^{-}$) for the NADPH-dependent reaction (Vogt 2010).

Lignan glycosides, such as the flax SDG ester-linked complex and the sesame seed sesamolin triglucoside, are hydrolyzed by some of the anaerobic microbes in the gut to lignan aglycones (Jan et al. 2009; Kim et al. 2006). The free lignans are then converted into enterolignans through a series of metabolic reactions by various gut bacteria (Clavel et al. 2006). 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 (Dagmar et al. 2010; Low et al. 2007).

The predominant plant lignan compound in foods, SDG, is metabolized in the gut to SECO, then to the enterolignan ED, and finally to EL, but the conversion is never 100%. The plant lignan MAT is metabolized directly in the gut to the enterolignan EL. In an in vitro fecal microflora metabolism system, lariciresinol was completely converted in 24 h into the enterolignans EL (46%) and ED (54%), whereas other plant lignans were incompletely converted, i.e., MAT (62%), SDG (72%), and pinoresinol diglucoside (55%). All four were metabolized to EL, in part, but SECO and pinoresinol diglucosides were converted to ED (50% of the SECO and 32% of the pinoresinol total doses) and then in small amounts to EL (21% of the SECO and 19% of the pinoresinol total doses) (Heinonen et al. 2001). Other lignans that are metabolized to EL include arctigenin, 7-hydroxymatairesinol, sesamin, and syringaresinol (Heinonen et al. 2001; Peñalvo et al. 2005). Smeds et al. (2006) found cyclolariciresinol, lariciresinol, and MAT but not SECO in serum samples from a Finnish population. Peñalvo et al. (2004) determined the presence of cyclolariciresinol, lariciresinol, MAT, pinoresinol, as well as anhydrosecoisolariciresinol, 7′-hydroxymatairesinol, SECO, and sesamin in plasma of Finns after the ingestion of sesame seeds (50 g).

The enterolignans ED and EL have been detected in the blood and urine of both humans and animals, but only small amounts of the plant lignans cyclolariciresinol, lariciresinol, MAT, pinoresinol, SECO, and syringaresinol have been found in human urine (Tarja et al. 2003). In contrast, lignins are thought to be largely inert and not absorbed in the human gut due to their polymeric nature. 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 (Begum et al. 2004). 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 (Horner et al. 2002).

EL is the main circulating enterolignan; therefore, serum EL levels and urinary EL excretion are used as biomarkers for plant lignan intakes. However, these are imperfect surrogates. Differences between lignan intakes and EL 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 EL, the redox state of the colon, the types of lignans present in the diet, and the use of antibiotics (Kilkkinen et al. 2001; Clavel et al. 2006).

#### 36.3.2.2 Systemic Metabolism

Once they are formed from the parent plant lignans by gut microbiota, the enterolignans ED and EL are absorbed through the colonic barrier (Jansen et al. 2005), and most are conjugated to glucuronides in the tissues. They are usually detectable in the blood 8–10 h after dietary intake (Clavel et al. 2006). In a recent study, some plant lignans (anhydrosecoisolariciresinol, 7′-hydroxymatairesinol, cyclolariciresinol, lariciresinol, MAT, pinoresinol, SECO, and sesamin) were rapidly absorbed in the small intestine and appeared in the systemic circulation within an hour after the ingestion of sesame seeds (Peñalvo et al. 2005). The mechanisms responsible for the uptake of plant lignans in the small intestine are still unknown (Lampe et al. 2006). 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 (Knust et al. 2006). Some free lignans and aliphatic or aromatic hydroxylated metabolites from hepatic metabolism may also be excreted (Knust et al. 2006; Lampe et al. 2006). One study found that the total amount of EL and ED detected in the urine was up to 40% of the ingested dose (0.9 mg/kg body wt, average 60–66 mg) of SDG and the majority of it was excreted within 2 days (Kuijsten et al. 2005).

The enterohepatic recirculation of SECO, 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 or in the liver prior to their appearance in the systemic circulation. Glucuronides and sulfates of SECO, EL, and ED may undergo enterohepatic recirculation or simply be eliminated in the bile or urine (Jan et al. 2010; Liu et al. 2006).

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 the lignan food frequency questionnaire validation study, conducted by Horn-Ross et al. (2006) using only MAT and SECO, the correlations with urinary total ED and EL were only 0.16. In the food frequency questionnaire validation study of Bhakta et al., the correlation of MAT and SECO "true intake" with plasma EL was only 0.11. Since several other lignans are present in the diet and can be converted to EL or ED 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.

## 36.4 Lignan Bioactivities

Lignans individually as well as in combination have been found to exhibit varied biological activities. What mechanisms underlie the activity of either the naturally occurring lignans or their derived metabolites? The antioxidant activity and the

estrogenic and antiestrogenic functions of lignans, as well as the influence of lignans on hormone metabolism and availability and on gene expression and/or enzyme activity, could all explain the effects of lignans. Some examples are provided in this section. Mainly ED and EL are responsible for these functions; thus the transformation of plant lignans by intestinal microbiota might be essential for these functions to be manifested (Landete 2012).

### 36.4.1 Antioxidant Activity

Some authors described the structure-activity relationships of lignans from *S. chinensis* in connection with antioxidant activity. Lee et al. (1999) studied the structure-activity relationships of lignans and their derivatives from *S. chinensis* as platelet-activating factor antagonists. In their study, 6,7- dehydroschisandrol A, a dibenzocyclooctadiene lignan, showed the strongest activity. The higher activity of lignans was observed in the absence of an ester group at C-6, a hydroxyl group at C-7, or a methylenedioxy moiety and the presence of an R-biphenyl configuration. Yim and Ko (1999) examined the protective effects of schisandrin A, schisandrin B, and schisandrin C against myocardial ischemia-reperfusion injury. The authors found that methylenedioxy group and the cyclooctadiene ring of the schisandrin molecule play as important structural determinants in the protection against myocardial ischemia-reperfusion injury. Choi et al. (2006) investigated the structure-activity relationships of the dibenzocyclooctadiene lignans in relation to their antioxidant activity. The study showed that the exocyclic methylene functionality was important for antioxidant activity of lignans. In addition, the presence of benzoyloxy group possibly improves such effects.

In some cases, antioxidant activity appears to be responsible for the bioactivity of plant and mammalian lignans. For example, beneficial effects of SDG in cancer and lupus nephritis revealed that these beneficial effects could be due to the ability of SDG to scavenge hydroxyl radicals (Prasad 1997), showing SDG to exert powerful antioxidant activity.

The antioxidant activity of flaxseed lignans and derived metabolites is because they exert protective effects against AAPH (2, 2′, azobis (2-amidinopropane) dihydrochloride), a compound used extensively as a free radical generator (Hosseinian et al. 2007; Hu et al. 2007). The flaxseed lignan SDG and mammalian lignans ED and EL act as antioxidants against DNA damage and lipid peroxidation. Plant lignan antioxidant activity has been attributed to the 3-methoxy-4-hydroxyl substituents of SDG and SECO, versus the meta mono-phenol structures of ED and EL. Benzylic hydrogen abstraction and potential resonance stabilization of phenoxyl radicals in an aqueous environment are likely to contribute to the antioxidant activity of the mammalian lignans. These probably represent extra- and intracellular antioxidant activities of flax-derived lignans at concentrations that are potentially achievable in vivo (Hu et al. 2007).

### 36.4.2 Estrogenic and Antiestrogenic Functions

Lignans and their derived metabolites ED and EL act either as estrogen agonists or antagonists. The chemical structures of these bi-phenolic compounds closely resemble that of endogenous 17β-estradiol, and they exert biphasic agonistic (estrogenic) and antagonistic (antiestrogenic) activities in vitro (Sathyamoorthy et al. 1994) and in vivo (Pauliina et al. 2011; Tou et al. 1999).

Research shows that physiologically relevant EL concentrations lead to in vitro and in vivo activation of estrogen receptor (ER)-mediated events and this has generated interest because of their potential use in hormone replacement therapy and cancer prevention (Hébert-Croteau 1998).

Because of their structural similarity to 17β-estradiol, enterolignans are natural ligands of ERs and are believed to be naturally existing selective estrogen receptor modulators. They might therefore act as anticarcinogens, either through antiestrogenic actions (e.g., by competing with estradiol to bind ERs) or by initiating their own anticarcinogenic effects (e.g., by recruiting specific transcriptional coregulators to phytoestrogen-activated ERs).

The mechanism of action of enterolignans on ER has been studied, and there is evidence from human observational studies that phytoestrogens may modulate hormone levels and ER expression (Touillaud et al. 2005). It is assumed that the biological action of phytoestrogen is mediated by ERα and ERβ. The ER is a ligand-dependent transcription factor belonging to the nuclear receptor superfamily. The ER binds estrogen response elements, a 13-bp inverted repeat, through its conserved DNA-binding domain. The ER contains two transcriptional activation domains: the autonomous transcriptional activation domain, AF-1, located at the N-terminus, and the ligand-dependent activation domain, AF-2, located at the C-terminus (Green and Chambon 1988); the primary sequence of AF-2 differs significantly between ERα and ERβ. This causes different agonist/antagonist characteristics for various chemicals containing phytoestrogens, depending on their affinity for the receptors (Barkhem et al. 1998). Carreau et al. (2008) examined and compared the ability of ED, EL, and 17β-estradiol to induce the transactivation of ERα and ERβ, to modulate ERα target genes. This study indicates that enterolignans have distinct properties for the transactivation of ERα and ERβ. ED, like 17β-estradiol, induces ERα transcriptional activation through transactivation functions AF-1 and AF-2, while EL is less efficient in inducing AF-1, acting mainly through AF-2. Furthermore, ED and EL modulate ERα mRNA and protein contents as well as MCF-7 cell proliferation.

EL, at physiological concentrations, activates ER-mediated transcription in vitro with preference for ERα. The effects of EL are mediated by the ER ligand-binding domain and are susceptible to antiestrogen treatment. Penttinen et al. (2007) demonstrated that EL exerts estrogenic activity in vivo. In transgenic estrogen-sensitive reporter mice, EL induces tissue-specific estrogen-responsive reporter gene expression as well as promotes uterine stromal edema and expression of estrogen-responsive endogenous genes (Cyclin D1 and Ki67). Taken together, these data show that

EL is a selective ER agonist inducing ER-mediated transcription both in vitro in different cell lines and in vivo in the mouse uterus.

Therefore, the transformation of plant lignans by intestinal microbiota might be essential for the estrogenic and antiestrogenic activity to manifest. Lignans and their derived metabolites have also been associated with a reduction in the risk of breast cancer through estrogenic and antiestrogenic effects. As above mentioned, the estrogen agonistic effect of ED and EL may be useful for conventional hormone replacement therapy in postmenopausal women. However, Pianjing et al. (2011) suggested that due to a potential tumor growth stimulation of lignans and their ability to induce certain estrogen-related genes, oral supplementation of enterolignans should be prescribed with caution, particularly in postmenopausal women and hormone-dependent breast cancer patients.

## 36.5 Health Benefits

Lignans are polyphenolic compounds with a wide spectrum of biological functions including antioxidant, anti-inflammatory, and anticarcinogenic activities; therefore, there is an increasing interest in promoting the inclusion of lignan-rich foods in humans' diets. The lignans consumed by human are in fact digested by the microflora present in the intestine. The weak and antiestrogenic effects of lignans are caused by distinct transactivation activities of estrogen receptors between the enterolignans ED and EL (Brito and Zang 2018). Previous researches indicate that certain conditions including breast, colon, and prostate cancer can be reduced by dietary lignan intake and/or increased levels of EL and/or ED. Clearly, more research is needed to determine causality and to evaluate the potential role of lignans and their metabolites in metabolic profiles.

### 36.5.1 Colon Cancer

ERs, especially the β-type receptors, are abundant in colon cells (Konstantinopoulos et al. 2003), where they play a role in normal colon functioning (Wada-Hiraike et al. 2006); however, cancer progression is associated with a loss of ER β (Castiglione et al. 2008; Jassam et al. 2005). This, together with data from epidemiological studies showing that hormone replacement therapy protects against colon cancer (Nelson et al. 1997), would indicate that EL has the potential to protect against colon cancer. EL may exert these potential effects both during absorption from the colon lumen and when passing the intestinal cells during systemic circulation.

Treatment of human colon cancer SW480 cells with EL and ED, either alone or in combination, resulted in dose- and time-dependent decreases in cell numbers (Qu et al. 2005). Cell growth inhibition by lignan metabolites seems to be mediated by cytostatic and apoptotic mechanisms (Ayella et al. 2010).

In a case-cohort study of Danish middle-aged men and women, which gathered detailed information on diet and lifestyle factors, Kuijsten et al. (2006) investigated

the association between plasma enterolignans and the incidence of colon and rectal cancer. The authors observed a substantial reduction in colorectal adenoma risk among subjects with high plasma concentrations of enterolignans, in particular, ED. Recently, Johnsen et al. (2010) examined the association between plasma EL concentration and incidence of colon and rectal cancer in 57,053 participants aged 50–64. They concluded that higher EL levels are associated with lower risk of colon cancer among women and higher risk of rectal cancer among men.

### 36.5.2 Breast Cancer

Some studies show that the administration of plant lignans, which are further metabolized to EL or EL as such, inhibit or delay the growth of experimental mammary cancer (Saarinen et al. 2010). The mechanisms underlying the anti-carcinogenic action of EL are not yet fully understood, but there is intriguing evidence for EL as a modulator of estrogen signalling. Sesamin is converted to the phytoestrogens and ELs. The phytoestrogens are known to play protective role against breast cancer (Peñalvo et al. 2005). Therefore, lignans and their derived metabolites have been also associated with a reduction in the risk of breast cancer through an estrogenic and antiestrogenic effect.

The results of the large prospective study of French women done by Touillaud et al. (2007) showed that higher dietary intakes of lignans were associated with a reduction in the risk of postmenopausal breast cancers. However, epidemiological studies that examined whether lignans protect against breast cancer have yielded inconsistent results. In this respect, Buck et al. (2010) conducted meta-analyses on the association between lignans and breast cancer risk. The meta-analyses included 21 studies (11 prospective cohort studies and 10 case-control studies), in which high lignan intake was associated with a significant reduction in breast cancer risk in postmenopausal women. Breast cancer risk was also inversely associated with enterolignan exposure but not with blood or urine EL concentrations.

### 36.5.3 Prostate Cancer

Lignans and their derived metabolites are believed to be partly responsible for growth inhibition of human prostate cancer cell lines (Demark-Wahnefried 2001). Morton et al. (2015) associated higher EL levels in prostatic fluid with a low risk of prostate cancer. In a small clinical study, prostate cancer cell proliferation decreased and apoptosis increased in men fed 30 g of flaxseed per day (Demark-Wahnefried et al. 2001). Other work by these authors further supports the role of flaxseed in combination with a low-fat diet as a means to control prostate growth (Demark-Wahnefried et al. 2004). In the study, prostate-specific antigen levels and cell proliferation both decreased from baseline after only 6 month on the dietary regime.

EL has been shown to inhibit prostate cancer growth and development, but the mechanistic basis for its anticancer activity remains largely unknown. Activation

of insulin-like growth factor-1 receptor signalling is critical for prostate cancer cell growth and progression (Chen et al. 2009).

### 36.5.4 Intestinal Cancer

Results by Pajari et al. (2006) demonstrate that MAT or SECO do not prevent intestinal carcinogenesis in MIN mice and that MAT may have adverse effects on intestinal carcinogenesis. The number of intestinal adenomas in the MIN mouse model is not related to plasma EL levels nor is it associated with the levels of intestinal lignans (Oikarinen et al. 2005).

### 36.5.5 Menopausal Symptoms

Phytoestrogens may be of use in ameliorating some menopausal symptoms. Results by Wu et al. (2006) suggest that sesame ingestion benefits postmenopausal women by improving blood lipids, antioxidant status, and possibly sex hormone status. On the other hand, epidemiological and pharmacological studies have shown that ED, and particularly its oxidation product EL, have preventive effects on osteoporosis and menopausal syndrome (Lemay et al. 2002).

### 36.5.6 Cardiovascular Disease

Flaxseed can protect against atherosclerotic plaque deposition in carotid arteries and shows anti-atherosclerotic effects in the aorta. The aforementioned authors show that dietary flaxseed can improve endothelium-dependent vascular relaxation in the presence of a high-cholesterol diet. Lignan intake may have an important protective effect against human vascular disease. Later, Dupasquier et al. (2007) demonstrated how dietary flaxseed can inhibit the atherogenic effects of a high-cholesterol diet in the LDLrKO mouse. However, the results by Kuijsten et al. (2009) do not support the hypothesis that high plasma ED or EL concentrations are associated with a reduced risk of nonfatal myocardial infarction. On the other hand, sesamin inhibits intestinal absorption of cholesterol and reduces the activity of acylCoA:cholesterol acyltransferase and 3-hydroxy-3-methylglutaryl CoA reductase in rats (Wu et al. 2006). Sesamin, at a rather low dose (65 mg/day or approximately equivalent to consuming 13 g of sesame seeds), lowers plasma cholesterol in subjects with hypercholesterolemia (Hirata et al. 1996).

### 36.5.7 Hepatoprotective Effects

Platelet-activating factor (PAF) has been linked to aggregation and degranulation of platelets and is an important mediator in inflammation and asthma. Plant lignans have been reported to exert anti-PAF activity (Tibiriçá 2010). Flaxseed

potentially inhibits several mechanisms associated with renal disease in lupus nephritis. Incorporating flaxseed into the diet of either an experimental mouse model of lupus, MRL/PR, or human lupus nephritis subjects demonstrated significant changes in renal and neutrophil function and plasma lipids (Westcott and Muir 2003). Doses above 30 g/day were not well tolerated mainly due to increased laxation. Use of purified SDG in the mouse model (MRL/lpr) showed that lignan was well tolerated and provided reno-protection similar to whole flaxseed (Clark et al. 2001). Ogborn et al. (2002) administered purified SDG and found that cystic change, epithelial proliferation, interstitial fibrosis, macrophage infiltration, and oxidant injury were all reduced (Ogborn et al. 2002). Recently, Moneim et al. (2014) have demonstrated how flaxseed oil may play a protective role against kidney injury.

Hepatoprotective effects have also been associated to lignans in a flaxseed supplemented diet. Hemmings and Barker (2010) found a hepatobeneficial effect of increased levels of γ-glutamyltranspeptidase (γGT) in the livers of both male and female rats. In addition, they reported that a diet with 10% flaxseed lacks long-term effects on growth, development, and behavior, is nontoxic, and may be hepatoprotective. SDG from flaxseed has been shown effective in preventing/delaying the development of type 1 and type 2 diabetes (Prasad 2002).

### 36.5.8 Neuroprotection

In regard to neuroprotective actions, Qin et al. (2014) reported that schisantherin A, schisandrin C, and schisandrol B were found to possess remarkable neuroprotective effects against serum and glucose deprivation injury in SH-SY5Y cells than schisandrin A, schisandrin B, and schisanhenol. The authors suggested that the number and position of a hydroxyl group and a methylenedioxy may be responsible for the neuroprotective effects of these lignans. Out of five dibenzocyclooctadiene lignans (deoxyschisandrin, gomisin N, gomisin A, schisandrin, and wuweizisu C) isolated from the methanolic extract of *S. chinensis*, deoxyschisandrin, gomisin N, and wuweizisu C markedly protected the glutamate-induced neurotoxicity in rat cortical cells (Kim et al. 2004). Song et al. (2015) studied the protective effects of schisandrin, schisantherin A, schisandrin B, and schisandrin C on amyloid-$\beta_{25-35}$- and homocysteine-induced neurotoxicity in PC12 cells. Among the four lignans, schisandrin B and schisandrin C effectively protected amyloid-β-induced neurotoxicity in PC12 cells by inhibiting the production of reactive oxygen species (ROS) and modulating the apoptotic signal pathway via Bax and caspase-3. Further, gomisins A, G, J, and N (schisandrin B) are strong inhibitors of toll-like receptor 2/4 (TLR 2/4) agonist-induced hyperneuroinflammatory responses (Young et al. 2014).

### 36.5.9 Anti-inflammatory Activity

Sesamin exhibited anti-inflammatory activity by inhibiting delta-5 desaturase, a key enzyme in arachidonic acid biosynthesis that leads to a reduction in the formation of

pro-inflammatory mediators (Chavali et al. 1998). An unusual tetrahydrofuran lignan from the roots of *Zanthoxylum planispinum* has also the potential anti-inflammatory effects (Su et al. 2016).

## 36.6 Application of Lignans in Food

### 36.6.1 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 (335 mg/100 g) and sesame seeds (373 mg/100 g), which have a lignan content a hundred times higher than other dietary sources (Julia et al. 2010). 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 present in fruits and vegetables such as asparagus, grapes, kiwi fruit, lemons, oranges, pineapples, wine, and even in coffee and tea (Kuhnle et al. 2009; Smeds et al. 2007).

In contrast to plants, there are virtually no lignans in animal foods. Minute amounts of the enterolignans ED and EL are sometimes found in animal foods (milk products) as a result of their production by bacterial metabolism in the animals' guts, but these are exceptions. Little has been done to investigate the effects of storage and processing on lignans in most foods (Kuhnle et al. 2009; Brenes et al. 2002), although it is known that the lignan content is apparently not changed considerably during the processing of flaxseed and sesame seed (Strandås et al. 2008; Wu 2007). Furofuran-type lignans are widely distributed in edible plants (flaxseed, sesame, seeds, cereal products, and *Brassica* vegetables). Sesame lignans in particular are obtained from *Sesamum indicum*, a highly prized oilseed crop cultivated widely in many countries in the east. The plant is the main source of clinically important antioxidant lignans such as sesamin, sesamolin, sesaminol, and sesamol.

### 36.6.2 Effect of Cooking on Lignans in Food

Plant foods or oils are used for preparing various foods like bakery products, chips, or blanched and cooked vegetables. During their production, the raw materials are heated to a lesser or greater extent, and the stability of lignans occurring in different conjugation patterns is influenced.

Roasting of sesame seeds at 200 °C for 60 min cleaved and liberated phenolic compounds (Jeong et al. 2010), and sesamolin could be degraded into sesamol (Lee et al. 2010). Infrared roasting of sesame seeds at 200 °C for 30 min also degraded sesamolin to sesamol (Kumar et al. 2010). In sesame oil the content of sesamol increased under heating conditions, while that of sesamolin decreased slightly, and

the sesamin content changed only little. For pinoresinol a high stability to thermal treatments below 180 °C was observed in olive oil (Brenes et al. 2002). However, a short microwave treatment already resulted in a small decrease (Cerretani et al. 2009). Kotsiou et al. (2009) reported that lignans like 1-acetoxypinoresinol remained unchanged during boiling or frying in olive oil. In pumpkin seeds, SECO was degraded by thermal heating with increasing roasting time (Murkovic et al. 2004). Hyvarinen et al. (2006) reported that the complex ester of SDG and SDG itself are stable in various bakery products. In flaxseeds, isolariciresinol, SECO, lariciresinol, and pinoresinol which were mainly present as esterified compounds were stable even if heated to 250 °C for 3.5 min. In contrast, pinoresinol aglycone in olive oil was degraded even at 180 °C (Carrasco-Pancorbo et al. 2010). This finding demonstrates that the type of conjugation and the matrix influence the thermal stability of lignans. To conserve a relatively high content of lignans during production of commercial foods, the raw product, the water content, and the applied temperatures have to be considered and optimized.

Moderate heating at 100 °C did not degrade the lignan aglycones and glycosides in dry foods. In contrast, heating was responsible for the better extractability of the lignans. If samples with high moisture content were heated, the degradation of the lignans in sesame seeds and rye was observed already at 100 °C. Higher roasting temperatures caused degradation of aglycones and glycosides.

## 36.7 Safety: Toxicity and Side Effects

A single-blind, placebo-controlled, parallel-group, and multiple oral dose study was conducted in 48 healthy subjects to investigate the pharmacokinetics and safety of multiple oral doses of sesame lignans (sesamin and episesamin). The results showed that sesamin was absorbed with a peak plasma concentration at 5.0 h. The plasma concentration of the main metabolite, SC-1, reached a peak at 5.0 h and decreased rapidly with a terminal half-life of 2.4 h. Episesamin was also absorbed with a peak plasma concentration at 5.0 h and decreased with a terminal half-life of 7.1 h. The plasma concentration of the main metabolite, EC-1, reached a peak at 5.0 h and decreased rapidly with a terminal half-life of 3.4 h. The plasma concentrations of sesamin and episesamin reached a steady state by day 7. Sesame lignans were confirmed to be safe and tolerable in healthy subjects (Namino et al. 2013). Niemeyer and Metzler (2002) reported that lignans resembled the isoflavone daidzein and differed from genistein and coumestrol, which exhibited clastogenic and gene mutagenic activity in V79 cells.

## 36.8 Marketed Products

Flaxseed can be incorporated into various food products to increase the intake of lignans. Traditionally, this has been done by adding flaxseed to bread either as whole seeds or in the form of ground flaxseed meal. However, the characteristic flavor of

flaxseed may limit its other applications in foods. More recently, the development of dehulling techniques has made it possible to separate a lignan-rich hull fraction from flaxseed (Hyvarinen et al. 2006), and several hull preparations are now commercially available. On the other hand, the possible presence of harmful substances such as cyanogenic glycosides and cadmium in flax has to be taken into account if the use of flaxseed in our diet is to be increased. Supplementation of bakery products with SDG isolated or enriched from flaxseed, thus, offers an attractive approach to be investigated.

## 36.9 Patents

Lignan Flax Seed Cakes offers consumers a delicious and simple way to consume ground flaxseed. This product combines multiple healthy ingredients, such as fruit, oats, and walnuts, with ground flaxseed to produce a well-textured and desirable food item. This comestible food product enables individuals to receive a known (controlled) quantity of flaxseed while simultaneously consuming other beneficial ingredients. The enjoyable taste makes it easy to obtain the health benefits provided by flaxseed within a consumer's diet.

The invention provides an enzyme having the lignan glycosidation activity by identifying an enzyme involved in the production of lignan glycosides, identifying an amino acid sequence of the enzyme polypeptide, and a base sequence encoding the polypeptide. Based on the information of these sequences, transformants capable of producing the lignan glycosides were prepared (Hyvarinen et al. 2006).

## 36.10 Perspectives

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 EL and chronic disease outcomes. Finally, it is of interest that most studies of lignan intake were of women, whereas all but one of the EL studies were of men. Because associations with lignans may vary by gender, 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.

The application of sesamin in auguring human health is one of the main themes of current research in medical science. Focus is required on validating the biological activities of furofuran lignans other than sesamin. Another point of concern at this juncture is to ensure the availability of sesamin in reasonable quantity for medical application, as sesame is the only major source of these lignans. Therefore, it may

be concluded that there is potential of a tremendous research on qualitative and quantitative improvement of the sesame crop for sesamin production. High-throughput analytical methods based on cell culture techniques would be a way out in advancing our knowledge on biosynthesis of sesamin both for productivity and human health.

Public acceptance of dietary products derived from transgenic organisms is limited. Nevertheless, lignans produced by transgenic hosts are chemically identical to natural ones and free from any recombinant genes or proteins. Thus, their public acceptance is expected to be more easily garnered than that of transgenic foods. Accordingly, more attention should be paid to the establishment of scaling-up and following industrialization of the lignan production systems (Satake et al. 2015). Large-scale lignan production by transgenic plants requires a closed cultivation system to prevent contamination of the environment by transgenic plants. Recently, various closed plant factories have been emerging, which completely shut off a gene flow into the outer environment and enable the transgenic plant-based molecular breeding of genes or compounds of interest under optimal and sterile conditions. Such advances in the metabolic engineering of lignan biosynthesis will surely pave the way for the conversion of conventional agricultural lignan production to innovative industrial lignan production.

## 36.11 Cross-References


- ▶ Antioxidants in Diets and Food
- ▶ Dietary Triterpenoids
- ▶ Lignans in Diets
- ▶ Phenylpropanoids (Phenylpropenes) in Diets


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