Journal of Natural Resources and Farming
https://doi.org/10.7770/jonraf-v2-art23

REVIEW

Lignans: phytoestrogens present in flaxseed (*Linum usitatissimum* L.) and their benefits to human health.

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Article history
Received: 12/12/2025
Accepted: 25/04/2026
Published: 06/05/2026

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ABSTRACT
Flaxseed (*Linum usitatissimun* L.) is a multipurpose oil crop valued for containing various beneficial functional ingredients. Lignans are a type of phytoestrogen that mostly exists as secoisolariciresinol diglucoside (SDG) in seed coat. SDG is transformed into different lignans in conjunction with bacterial glucosidase. This revision, therefore, documents the composition of the lignans present in flaxseed hull and its positive effect on human health. This state of art examines from the metabolic pathway involved in lignans synthesis and their mechanisms of joining with ER estrogen receptors to induce a response in humans. It also analyses the effects of ingestion of flaxseed on human beings. Finally, lignans intervene in gene transduction in conjunction with ER by stimulating positive responses to human vital functions. Overall, the extensive evidence supporting lignans benefits to human health should increase flaxseed consumption in global population.

Keywords: Lignans, Phytoestrogens, Antioxidant, Seed, Linum usitatissimum , Health.

Introduction

Flaxseed (*Linum usitatissimum* L.), known as linseed, has been used as a source of food and fiber since prehistoric times, concentrated in Asia, North Africa, and Europe (Daun et al., 2003; Morris and Vaisey-Genserb, 2003; Oomah, 2003; Wanasundara and Shahidi, 2003; Hall et al., 2006).

Currently, flaxseed is cultivated in more than fifty countries, primarily in the Northern Hemisphere, with the Russian Federation being the world's leading producer with 1.5 million hectares and the largest exporter at 600 tons (FAO, 2021). At the national level, Chile is characterized by a production that is mostly for self-consumption, and commercial needs are met through exports from Argentina and Canada.

There is a growing interest in consuming flaxseed (*Linum usitatissimum* L.) due to its beneficial health properties. It has been shown to have anti-hypercholesterolemic, anti-carcinogenic, and glucose metabolism-regulating effects, aiding in the prevention of diseases such as hormone-dependent cancers, diabetes, and lupus. This interest stems from the discovery that flaxseed increases lignan production in mammals (Babu and Wiesenfeld, 2003; Oomah, 2003; Thompson, 2003; Shearer and Davies, 2005).

Interest in this oilseed is increasing global demand for flaxseed according to the Food and Agriculture Organization's Corporate Statistics Database (FAOSTAT, 2023), the global harvested area increased by 31% in 2021, from 3.14 million hectares in 2018 to 4.14 million hectares.

Flaxseed is 4 to 6 mm long, flattened, and oval, its color can vary from dark brown to light yellow, and it has a pointed edge with a sticky texture (Daun et al., 2003). It has two flattened cotyledons, while the embryo is surrounded by a layer of endosperm and protected by the seed coat. The seed coat has three layers: an outer layer where most of the soluble fibers are stored, and two inner layers containing fiber and lignans. In percentage terms, the seed is divided into 57% cotyledons, 21% endosperm and 22% testa (Daun et al., 2003; Oomah, 2003; Wiesenborn et al., 2003).

Flax seeds are chemically composed of 40% lipids, with 87% of these distributed in the cotyledons and 17% in the endosperm. They contain 20% protein, distributed as 76% in the cotyledons and 16% in the endosperm, and 30% dietary fiber. They are rich in polyunsaturated fatty acids such as alpha-linolenic acid (ALA), or omega-3, and linolenic acid (LA), or omega-6 (Babu and Wiesenfeld, 2003; Daun et al., 2003; Oohma, 2003). These latter fatty acids are important for humans because they cannot synthesize them on their own (National Institutes of Health, 2022).

Regarding the types of fibers provided by flaxseed, these include cellulose, mucilage, and lignin. Lignin is related to lignans, a very important phytoestrogen in the human diet that helps in cancer prevention (Safe, 2006). In addition, flaxseeds have antifungal and antiviral properties and can inhibit enzymes of this nature (MacRae and Towers, 1984; Modolo et al., 2011; Patel et al., 2012). Flaxseeds contain three types of phenols: phenolic acids, flavonoids, and lignans. These substances can be found in esterified form and contribute to the plant's color and pollination, with beneficial health characteristics (Daun et al., 2003; Hall et al., 2006; Muir, 2006).

Lignan is a diphenolic compound with a 2,3-dibenzylbutane chemical structure, formed through the dimerization of coniferyl alcohol (Yang et al., 2001). Flaxseed, being the richest plant source of lignans (Thompson, 2003), primarily produces secoisolariciresinol diglucoside (SDG), with lignan being the main component (Landete, 2012). These lignans are consumed in conjunction with gastric acid and bacterial glucosidase present in the digestive tract, transforming into enterodiol (END) and enterolactone (ENL), the so-called

mammalian lignans. The structure of lignans includes oxo, keto, hydroxyl, and methyl ester groups, which make them hydroxyl radical scavengers (Figuerola et al., 2008). This characteristic gives it a structural similarity to 17-β-estradiol, allowing it to bind to estrogen receptor compounds in cells and exert both estrogenic and antiestrogenic effects (Martin et al., 1978; Wang et al., 1996; Kuiper et al., 1998; Miksicek, 1994). This may contribute to protection against colon cancer, prostate cancer in men, and breast cancer in women (Raffaelli et al., 2002). Furthermore, enterodiol (END) serves as a risk biomarker for identifying the development of these types of cancer and cardiovascular diseases (Wang, 2002).

Lignans can act as estrogen receptor antagonists (anti-estrogenic response) or agonists (estrogenic response), or they can exhibit a selective agonist/antagonist response, which is influenced by certain factors (Elena et al., 1998; Montana and Katezenellebogen, 1997).

The antagonistic effects of lignans may contribute to the prevention of coronary heart disease and hormone-dependent cancers such as breast, prostate, uterine, and ovarian cancer. On the other hand, their agonistic effects could be beneficial for managing osteoporosis (Chiechi, 1999). All the above provide background information demonstrating how lignans play an important role in the relationship between diet and hormone-dependent cancers (Adlercreutz et al., 1986; Boccardo et al., 2004).

The properties of this seed and the studies conducted indicate that its effects, both on the diet of those who consume it regularly and on its contribution to reducing the risk of coronary heart disease and some types of cancer, are effective. Therefore, this review aims to document the composition of lignans present in flaxseed (*Linum usitatissimum* L.) and their positive effects on human health from recent decades and cutting-edge research to delve deeper and demonstrate the real impacts of this seed on human health.

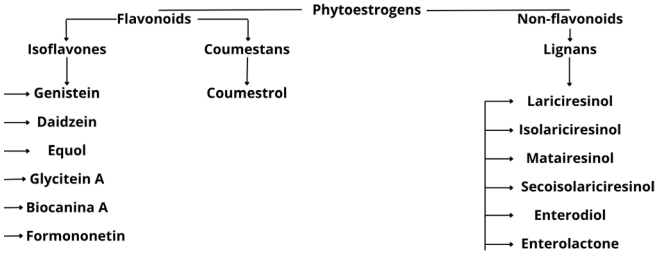
Lignans

The Food Standards Agency stated in 2003 that phytoestrogens are "any plant substance or metabolite that induces biological responses in vertebrates and that can mimic or modulate the actions of endogenous estrogens, usually by binding to estrogen receptors". These compounds are found in numerous plant-based foods such as cereals, legumes, fruits, and vegetables (Thompson et al., 1991).

Lignans are plant-derived chemical phytoestrogens that have a structure like the human estrogen hormone. The main phytoestrogens are isoflavones, coumestans, and lignans (Figure 1) (Martin et al., 2007; Food Standards Agency, 2003). According to Meagher and Beecher (2000), flaxseed has the highest concentrations of secoisolariciresinol (SECO) (28,000–369,000 μg/100 g) of any food. It also contains other lignans such as matairesinol, pinoresinol, lariciresinol, isolariciresinol, and secoisolariciresinol diglucoside (SDG) (Thompson and Boucher, 2006).

Figure 1.

The relationship between the different groups of phytoestrogens and their members of each group.



Adapted from Food Standards Agency, 2003

Lignan Metabolism

The main lignan in flaxseed is secoisolariciresinol diglucoside (SDG), which is in a linked macromolecular structure (Muir and Westcott, 2003; Suzuki and Umezawa, 2007; Struijs, 2008; Touré and Xueming, 2010; Schmidt et al. 2012). It is suggested that lignans are synthesized in the seed coat since hull contains higher amounts of lignans than the whole seed (Oomah and Mazza, 1997; Madhusudhan et al., 2000; Wiesenborn et al., 2003; Struijs et al., 2006).

Lignan biosynthesis in flaxseed occurs via four main pathways including phenylpropanoid, stereo-specific coupling by directing proteins, dibenzylbutane biosynthesis and lignan glycosylation (SDG) (Figures 2 and 3) (Umezawa, 2003; Hano et al., 2006; Struijs, 2008; Ghose et al., 2004).

Phenylpropanoid Pathway

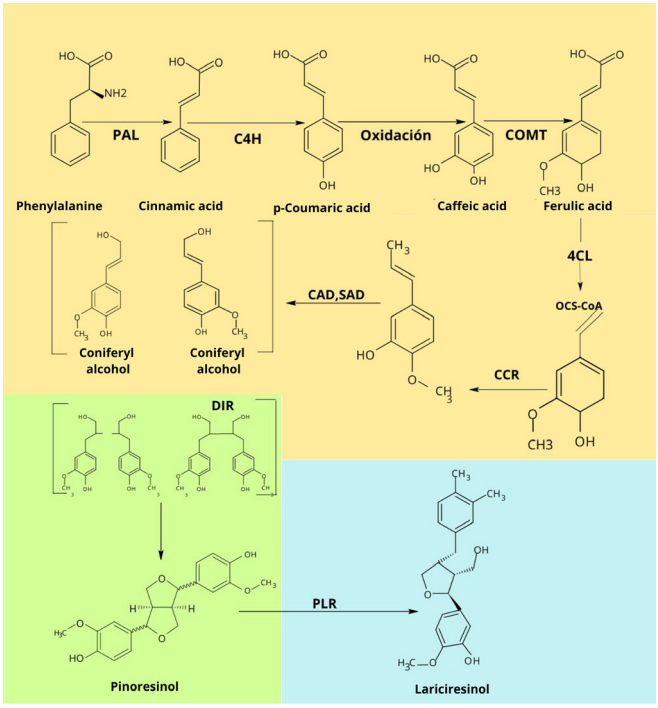
This pathway is responsible for forming the basic unit of lignans, C6-C3, through the deamination of phenylalanine-by-phenylalanine ammonia lyase, which produces cinnamic acid (Struijs, 2008). This acid is oxidized to p-coumaric acid, which is then oxidized to caffeic acid, which is metabolized to ferulic acid by acid O-methyltransferase. Ferulic acid is converted to its coenzyme A-activated form, feruloyl-CoA, by 4-coumarate:CoA ligase. Feruloyl-CoA is reduced to coniferaldehyde by cinnamoyl-CoA reductase and finally transformed into coniferyl alcohol by alcohol dehydrogenase and sinapyl alcohol dehydrogenase (Boerjan et al., 2003).

Stereospecific Coupling by Leading Proteins

The discovery in Forsythia species was that two phenylpropanoid monomers, coniferyl alcohols, were oxidized in the presence of the insoluble fraction of the Forsythia stem, producing pinoresinol (Umezawa et al., 1990). Subsequently, a purified protein from the insoluble fraction of the stem was used to catalyze the dimerization of coniferyl alcohols in the presence of a single oxidase; this was termed a leading protein because it is not involved in the reaction (David et al., 1997; Corbin et al., 2018).

Figure 2.

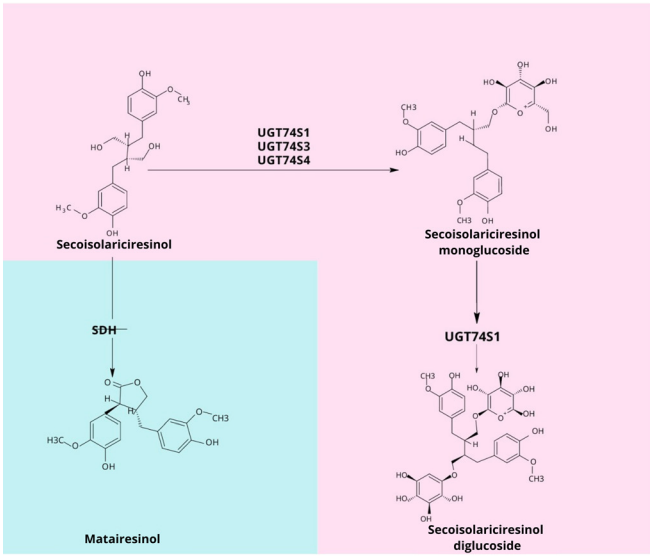
Phenylpropanoid pathway.



(Yellow): PAL, phenylalanine-ammonia lyase; C4H, cinnamate 4-hydroxylase; COMT, caffeic acid O-methyltransferase; 4CL, 4-coumarate: CoA ligase; CCR, cinnamoyl-CoA reductase; CAD, cinnamyl alcohol dehydrogenase; SAD, sinapyl alcohol dehydrogenase. Stereospecific coupling. (Green): DIR, leader protein. Dibenzylbutane biosynthesis. (Blue): PLR, pinoresinol/lariciresinol reductase; SDH, secaisolariciresinol dehydrogenase. (Adapted from Umezawa, 2003; Hano et al., 2006; Struijs, 2008; Ghose et al., 2004).

Figure 3.

Dibenzylbutane biosynthesis.



(Blue): PLR, pinoresinol/lariciresinol reductase; SDH, secaisolariciresinol dehydrogenase. Lignan glycosylation (SDG). (Pink): UGT74S1, UGT74S3, UGT74S4, uridine glucosyltransferases (UGTs). (Adapted from Umezawa, 2003; Hano et al., 2006; Struijs, 2008; Ghose et al., 2004).

The discovery of the directing protein provided insight into the coupling of phenolic radicals, an oxidase forms two radicals from alcohols, and the directing protein aligns the consecutive radicals through a stereoselective coupling reaction (Davin et al., 1997; Davin and Lewis, 2000). Of all the basic units formed by the phenylpropanoid pathway, only coniferyl alcohols can dimerize in a stereospecific manner (Davin et al., 1997).

Dibenzylbutane biosynthesis

In this pathway, pinoresinol is converted to lariciresinol and secoisolariciresinol by a bifunctional, NADPH-dependent pinoresinol/lariciresinol reductase (PLR) (Ford et al., 2001). PLRs first convert pinoresinol to lariciresinol, and then lariciresinol is converted to SECO (Von Heimendahl et al., 2005; Hemmati et al., 2007). The lignan matairesinol is formed by secoisolariciresinol dehydrogenase (SDH) (Ford et al., 2001; Xia et al., 2001; Umezawa, 2003; Struijs, 2008).

Lignan glycosylation (SDG)

The final step in the biosynthetic pathways is glycosylation catalyzed by GTs, which are highly divergent, polyphyletic, and belong to a multigene family (Mackenzie et al., 1997; Barvkar et al., 2012). In plants, they belong to the 1GT family, known as uridine GTs (UGTs) (Caputi et al., 2012; Wang and Hou, 2009; Fofana et al., 2017). UGTs catalyze the transfer of UDP-activated sugars to specific molecules (Jones and Vogt, 2001; Ross et al., 2001; Witte et al., 2009).

In plants, they are distinguished by a plant secondary product glycosyltransferase (PSPG) box composed of forty-four amino acids (Paquette et al., 2003; Gachon et al., 2005; Barvkar et al., 2012). They possess a catalytic mechanism that inverts the anomeric configuration of the sugar (Wang and Hou, 2009; Barvkar et al., 2012).

In *L. usitatissimum*, 137 UGT genes have been identified (Barvkar et al., 2012). The expression of the *UGT74S1* gene is particularly high in the seed coat, due to the high concentration of SDG available in flax seeds (Hano et al., 2006). The reaction of purified proteins with UDP and SECO glucose showed that only UGT74S1 produced SECO monoglucoside (SMG) and SDG metabolites, this demonstrates the participation of UGT74S1 in SECO glycosylation to form SDG lignans (Ghose et al., 2014).

Estrogenic activity of lignans

In the human body, estrogens are steroid hormones responsible for the development and growth of female reproductive organs. They also influence bone growth and fat metabolism (Ganong, 1990). Dietary lignans may offer protection against breast cancer in women, prostate cancer in men, and colon cancer (Raffaelli et al., 2002). This protective effect is attributed to their ability to compete with estradiol for the type II nuclear receptor and induce sex hormone-binding globulin (SHBG) (Wang, 2002).

SHBG is the main plasma sex hormone transporter protein, exhibiting a high affinity for endogenous estrogens. Its mechanism binds a portion of circulating testosterone

and, to a lesser extent, estradiol. The unbound fraction of circulating steroid becomes the active species that penetrates cells to bind to specific receptor proteins, creating a hormone reservoir protected from renal clearance and metabolic conversions. This characteristic allows it to have a longer half-life than a peptide bond (Best and Taylor, 1986).

SHBG production occurs in the liver, and its ability to bind to estrogens can alter the levels of estrogens available to target cells (Mousavi and Adlercreutz, 1993). Some phytoestrogens can inhibit the formation of human hepatocellular carcinoma cells in vitro. The control of cell proliferation may be due to the ability of phytoestrogens to enhance SHBG levels, increasing their binding to free estrogen and decreasing the levels of free estrogens available to tumor cells (Wang, 2002). This suggests that fiber-rich foods containing lignan precursors, through the production of END and ENL in the intestinal tract, can stimulate SHBG synthesis in the liver, reducing plasma levels of free hormones (Martín et al., 1996). In men, approximately half of circulating testosterone, as in pregnant women, and approximately 88% of total estrogens, are bound to SHBG (Dunn et al., 1981).

Enzyme Inhibition

The main mammalian lignans are enterodiol (END) and enterolactone (ENL). END inhibits some steroid cell metabolic enzymes, such as aromatase (Winer et al., 2005). This enzyme catalyzes the conversion of androgens to estrogens in multiple tissues and may play a role in the development of breast cancer.

Estrogens

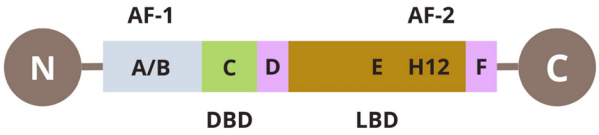
Estrogens are steroid compounds, produced primarily in the ovaries, but also in the testicles and adrenal cortex, where they perform various physiological functions. Estrogens are classified into two categories based on their origin: endogenous and exogenous. Endogenous estrogens originate naturally in glands or cells of the body; this category includes animal estrogens and plant phytoestrogens (Flasch et al., 2022). Exogenous estrogens, on the other hand, are synthetic (Ohta et al., 2015). In humans, four types of estrogens have been identified: estrone (E1), 17β-estradiol (E2), estriol (E3), and estetrol (E4) (Kumar and Goyal, 2019). These estrogens influence crucial functions in the regulation of the cardiovascular system, liver, pancreas, bones, and immune system (Faltas et al., 2020).

Estrogen Receptors (ERs)

In mammals, there are two estrogen receptors (ERs), ERα and ERβ (Hewitt et al., 2016). These receptors belong to the nuclear receptor family, meaning they function in the cell nucleus and act as receptors for various hormones. They share a multidomain structure; ERs have six A-F domains (Gibson and Saunders, 2012). Each domain encodes structural features, as shown in Figure 4.

Figure 4.

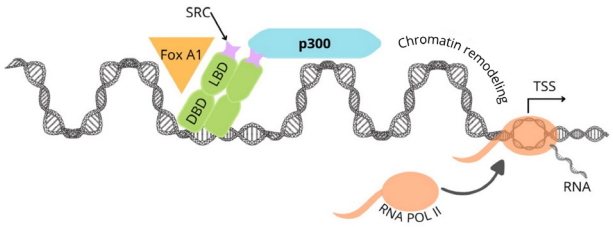
Diagram of domains A to F.



Starting from the amino (N) to the carboxyl (C) end. AF-1 and AF-2 mediate transcriptional activity, DBD interacts with ERE DNA and LBD binds to E2, H12 interacts with transcriptional activators and repressors (Adapted from Hewitt and Kenneth, 2018).

Figure 5.

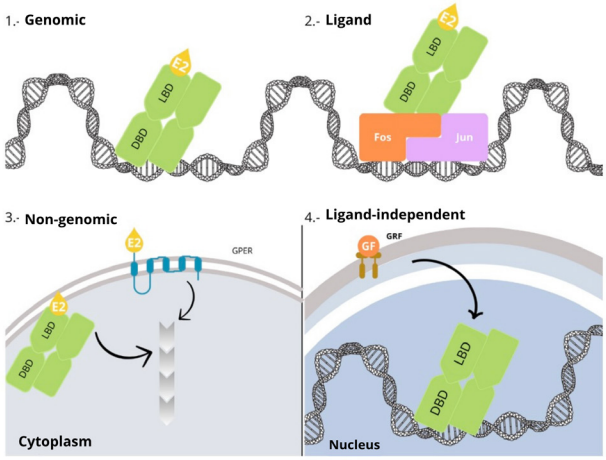
Regulation of ER-mediated transcription.



The pioneer factor such as FOX A1 (Orange triangle) indicates more open areas in the chromatin facilitating the access of the ER (Green) to the DNA ERE, the interaction of E2 ended up recruiting coactivator molecules of the steroid receptor (SRC) in the ER and interacts with p300, the chromatin remodeling activity of p300 facilitates the assembly of RNA Pol II in the TSS, leading to increased RNA transcription of ER target genes (Adapted from Hewitt and Kenneth , 2018).

Figure 6.

Mechanism of action.



The literature describes four mechanisms of action. (1) The genomic mechanism demonstrates the interaction between DNA ER and ERE. (2) the mechanism linking indirect interaction between ER and transcription regulators such as AND AP-1 that binds to FOS/JUN money. (3) the non-genomic mechanism shows us how a signal from extracellular E2 produces signal cascades in the cytoplasm; in this mechanism no genomic interactions are observed. (4) the ligand-independent mechanism acts in the transduction of extracellular growth factor (GF) activation in the membrane (GFR), where the triggered signals are received by the ER activating the transcriptional modulation of target genes (Adapted from Hewitt and Kenneth, 2018).

The longer A/B domain is involved in transcriptional activation (AF)-1 by interacting with transcriptional coregulators, helping to maximize RNA rates. It also has intrinsic disordered regions that confer flexibility in ER response functions, interacting with other ER domains (Hilser and Thompson, 2011). The C/DBD domain includes two zinc structures, which are formed by the chelation of zinc cations with four cysteine residues (Aagaard et al., 2011). The D/hinge region contains part of the C/BDB domain and sequences important for the nuclear localization of the ER protein (Sentis et al., 2005). The E/LBD domain, where LBD folds, is a complex structure with eleven α-helix formations, which form a high-affinity interaction site with E2 (Kumar and McEwan, 2012).

Finally, the F domain represents exclusive characteristics of ERs, such as the carboxyl terminus, as well as their intramolecular interaction and stability (Arao and Koraj, 2018). According to the ER type, these are expressed in different tissues and organs in humans. ERα is expressed in reproductive tissues: uterus, ovaries, bones, kidney, liver, and breast, among others, while ERβ is expressed in male reproductive organs, the central nervous system (CNS), the cardiovascular system, lungs, the immune system, colon, and kidneys (Jia et al., 2015).

The binding of LBD to E2 initiates structural transformations in the ER protein. This action allows the interaction of E2/ER and its transcriptional coactivators, as shown in Figure 5. These ER functions incorporate variations in the mechanisms, which are classified as genomic, ligand-independent, non-genomic, and ligand-independent.

The mechanisms shown in Figure 6 each have a distinctive feature. The genomic mechanism originates through a direct exchange between ER DNA motif dimers and estrogen-sensitive elements (ESEs). The ligand-mediated mechanism involves indirect interactions of DNA that anchors or binds to ER proteins in a DNA transcriptional response with the help of FOS/JUN binding, a method used in in vitro systems (Safe et al., 2008). The non-genomic signaling mechanism is the interaction between E2 and cell membrane receptors, either through the ER itself or with the help of a G protein-coupled receptor (ER1) or (GPER) (Levin, 2015). Finally, the ligand-independent mechanism refers to the effects observed from ER induction on the activation of other pathways, resulting in ER-mediated transcriptional responses independent of estrogenic steroid ligands (Hewitt et al., 2017).

Studies on the effects of flaxseed

Flaxseed lignans demonstrate the ability to interfere with the phenotype of the malignant tumor, which affects its cellular characteristics. In addition, flaxseed lignans, by affecting connections in molecular signaling networks, modulate signaling cascades in various stages of cancer (Nowak and Jeziorek, 2023).

The Western diet has focused on lignans as potential chemopreventive agents, with the most abundant plant lignans found in flaxseed and sesame (Milder et al., 2005). The effects of flaxseed on prostate cancer prevention in primary and secondary settings, using a flaxseed-supplemented diet, were examined in two studies. The first study investigated patients scheduled for surgery, whose diet consisted of consuming 30 g of ground flaxseed daily for 34 days. A decrease in tumor proliferation and tumor apoptosis rates was observed, with a significant difference between the initial and final patient assessments (Demark-Wahnefried et al., 2001).

The second study analyzed the effect of flaxseed supplementation with a low-fat diet compared to the patients' usual diet. Both groups were administered 30 g of flaxseed over a period of 21 to 32 days, resulting in significant reductions in tumor proliferation (Demark-Wahnefried et al., 2008). These studies indicate that diets rich in lignans have the potential to serve as cancer biomarkers, affecting tumor proliferation in a dosage dependent manner (Saarinen et al., 2010).

The determination of a single intake dose of flaxseed is not yet regulated; further studies are needed to verify the effect of lignans on physiological processes. Some studies indicate that doses of flaxseed exceeding 1 mg/kg of body weight are necessary to inhibit carcinogenesis (Saarinen et al., 2008). Furthermore, the consumption of soy foods reduces the risk of breast cancer in Asian women (Wu et al., 2008). In our country, 400 mg flaxseed capsules are available, with a recommended intake of two capsules per day (Bootic, 2023).

Conclusions

The various findings described in the literature suggest that flaxseed is safe and intervenes in biological alterations such as transduction where the union of the ER that are expressed in various organs, helps lignans to manifest themselves in different vital functions of the human being.

This review highlights the mechanisms of action of lignans and how their expression, in conjunction with endocannabinoids (ERs), demonstrates their fundamental importance in a regular diet.

Therefore, further studies are needed to investigate the role of lignans in their interaction with ERs and how they contribute to the expression of hormone-dependent diseases.

The anti-term effect of lignans play an important role in medicine and have also prompted the industrial production of lignans using synthetic biology. SDG is the most abundant lignan in flaxseed, and its synthesis pathway is well-studied. However, there is limited research on the transcription factors that regulate the key enzymes of the pathway, and the downstream pathways of SDG metabolism remain largely unexplored. These open opportunities to further investigate by multi-omics approaches how lignans interact with specific genes at the transcriptional and metabolomics level that certainly will shed light in our understanding of lignans action and crosstalk regulation of important pathways responding to diet, lifestyle, and different types of cancer in human beings.

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