# Biological Properties of Lignans

Subjects: Plant Sciences

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Lignans are, phenolic compounds and, as such, have a strong antioxidant capacity, which inextricably links them to beneficial effects on human health. Flax (*Linum usitatissimum*) is an annual herbaceous plant with blue flowers, widespread in various parts of the world. Flaxseeds are one of the plant matrices richest in lignans.

flaxseed lignans secoisolariciresinol diglucoside (SDG)

## 1. Introduction

Flax (*Linum usitatissimum*) is an annual herbaceous plant with blue flowers, widespread in various parts of the world. Its Latin name means "very useful" and, throughout human history, this plant has been used for very different purposes, as a fiber plant and oil crop. The flax seed consists of an embryo, two cotyledons, and a hull, in the approximate proportions of 4%, 55%, and 36%, respectively. Flaxseed hulls can vary in color from yellow to brown. The difference in pigment does not involve variations in proximate composition, functional properties, or biological activities [1].

Flaxseeds are rich in fats, particularly polyunsaturated fatty acids (around 70% of total fats). Linolenic acid, an omega-3 fatty acid with beneficial health properties, is the prevalent polyunsaturated fatty acid [2].

The chemical composition of flax seeds depends mainly on the cultivar, harvest time, geographical origin and post-harvest processing method [3][4]. Most of the lipids and proteins are concentrated in the cotyledons, while the flaxseed carbohydrates are condensed in the hulls [5]. As for micronutrients, flax seeds have a high amount of minerals (especially potassium), vitamins E and B3 [2], and phenolic compounds [6].

Flaxseeds are of great interest to the food industries because of their functional properties [7]. They give particular sensory characteristics to foods, when used as ingredients during processing, storage, and use as additives [6][8]. Adding flaxseeds to packaged products such as bread, cookies, bars, soups, and snacks has been shown to confer functional properties to these products, increase their shelf-life, and enhance sensory characteristics valued by consumers. Flaxseed addition, however, should not exceed 20% so as not to adversely affect the texture, normal gluten behavior, and overall acceptability by consumers who do not like an excessive nutty taste in such products [9].

Regarding flaxseed oil, it has excellent functional properties, as it slows down the oxidation process and prevents rancidity in products to which it is added, but it is used in moderation because it is easily prone to oxidative degeneration [10].

Of great interest is flaxseed mucilage or gum, known for its probiotic qualities and high capacity to bind water and retain moisture. These characteristics make it an ideal ingredient to increase the consistency, viscosity, and stability of some beverages and stabilize some pork-based foods [11]. It is used more than other food gums because less is needed to achieve the same degree of texture in the food [12].

However, alongside the nutritional and beneficial compounds, flaxseeds have compounds with toxic or antinutritional effects. There are cyanogenic compounds with potential toxicity for humans and animals and antinutrients such as linatine and phytic acid [12][13].

Flaxseeds are one of the plant matrices richest in lignans. Lignans are a heterogeneous group of molecules found in almost all higher plants [14] belonging to the phytoestrogen family, which also includes other molecules such as isoflavones, coumestans, and flavonoids [15]. Lignans play a role in the defense of the plant and seeds against diseases, pathogens, and herbivores [16].

Chemically, although the structural model may differ, they are formed by two phenylpropane units (C6-C3) linked by their carbon 8 with a β-β' bond, so they are generically referred to as diphenolic compounds or phenylpropanoid dimers [14][17]. These phenylpropane units are often called "monolignols": the most common are the p-coumaryl, coniferyl, and synapyl alcohols, which differ in the methoxylation on the aromatic ring [14]. In particular, coniferyl alcohol is found predominantly in the cell walls of plant tissues [18]. The polymerization of monolignols gives rise to natural lignin, a molecule characteristic of woody plants [14].

Various types of lignans can be formed depending on the bonding between different phenylpropane units. Based on the cyclic structure, carbon skeleton, and oxygen position, eight groups of lignans have been identified: furofuran, furan, dibenzylbutyrolactone, dibenzylbutane, dibenzylcycloctadiene, dibenzylbutyrolactone, arylnaphthalene, and aryltetralin [17].

Lignans are molecules widely distributed throughout the plant kingdom, although some plants synthesize higher amounts in different parts of the plant (roots and seeds). Cereals, fruits, and vegetables contain low levels of lignans, while flax and sesame seeds have higher concentrations, especially flax seeds. It has been estimated that the amount of lignans present in flaxseed is 75 to 800 times higher than in cereals, legumes, fruits, and vegetables [3].

The applications of lignans are numerous thanks to their beneficial and nutritional properties as antioxidant, anti-inflammatory, and anticancer agents. They are used in the food industry as ingredients in functional foods and beverages or as food supplements [19]. They enter as constituents in cosmetics and toiletries, such as for hair or skin care [20]. Lignans are also used as active ingredients in pharmaceutical products [21][22].

The global market for lignans is projected to reach over 90 million US Dollar by 2026 [23]. Diseases due to inadequate lifestyles are progressively increasing, and therefore it is foreseeable that consumer demand for food supplements, in particular, flaxseed, will increase, especially in light of their numerous beneficial effects on human health [16].

## 2. Biological Properties of Lignans

Lignans are, as mentioned, phenolic compounds and, as such, have a strong antioxidant capacity, which inextricably links them to beneficial effects on human health [5]. Moreover, secoisolariciresinol (SECO), like the other lignans found in flaxseed (matairesinol, lariciresinol, and pinoresinol), are mammalian estrogen precursors that are converted to enterolignans, enterodiol, and enterolactone (**Figure 1**), by the anaerobic intestinal microflora [24].

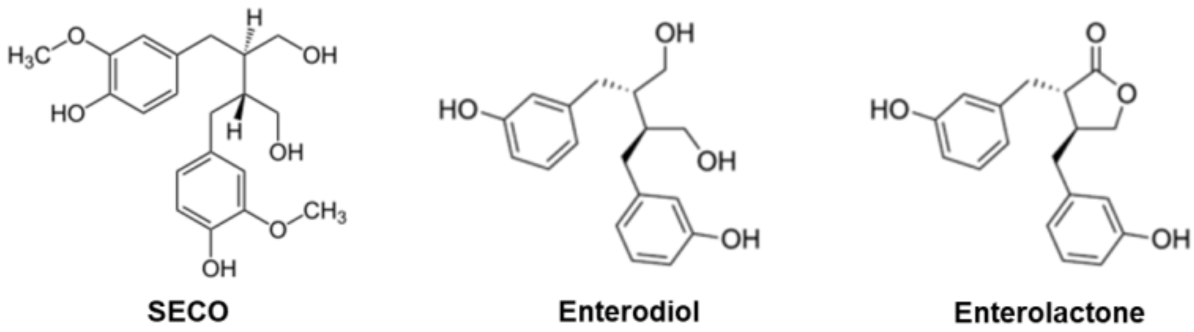


**Figure 1.** Secoisolariciresinol (SECO), precursor of enterodiol and enterolactone.

Lignans are now recognized as anticholesterol [25][26][27], antiviral [28], anticancer [29][30], antioxidant [7][31], supplemental for improved athletic performance [32], antidiabetic [33][34], estrogenic and anti-estrogenic [35][36], anti-inflammatory [37], anti-depressant [38][39], anti-bacterial, and anti-fungal [40]. **Figure 2** summarizes the main beneficial effects of lignans.

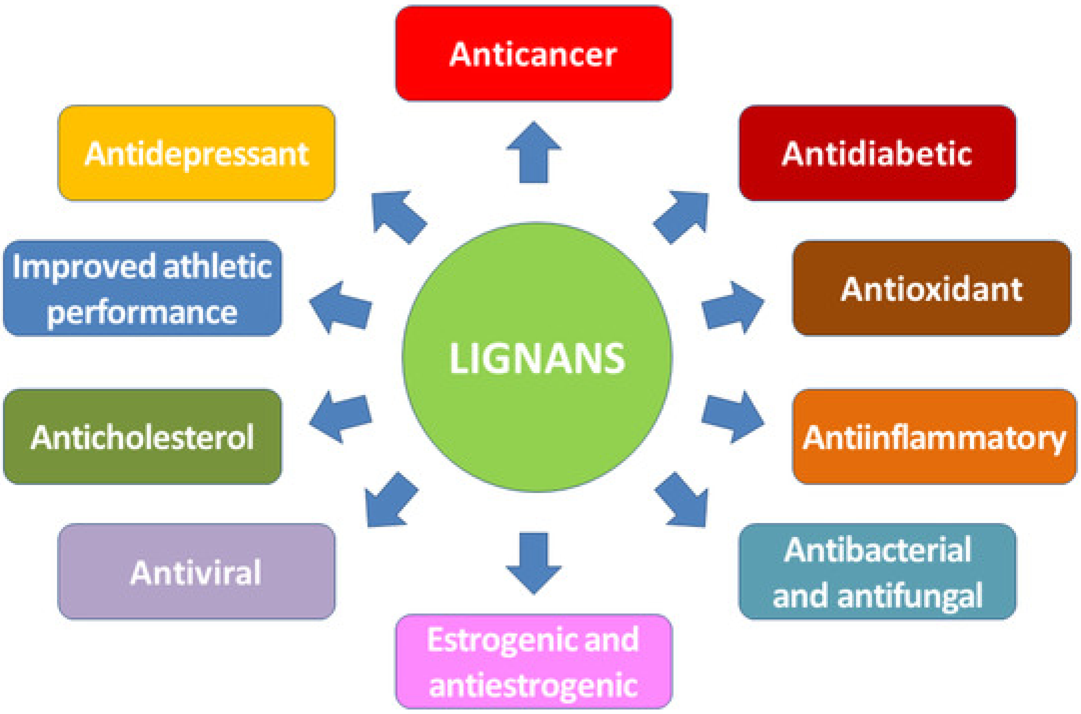


**Figure 2.** Beneficial properties of lignans.

Due to their phenolic characteristics, lignans play an essential role as “scavengers” of hydroxyl radicals, which makes them a valuable defense against the development of diseases caused by the free radicals produced by the human body during the oxidation of fats, proteins, and carbohydrates. Free radicals damage tissues, membrane lipids, nucleic acids, and proteins and can cause cancer, lung disease, neurological disease, premature ageing, and diabetes [3].

Due to their similarity to mammalian estrogens, lignans can help treat cancers related to hormone metabolism [18]. They can bind to estrogen receptors, altering the functionality of estrogens, in particular, lowering their circulation in the bloodstream and their biological activity, thus reducing the risk of developing cancer [3]. Their mechanism of action would actually appear to be much more complex, as they can, for example, influence intracellular enzymes and protein synthesis, stimulate the production of sex hormone-binding globulin in the liver, and reduce the concentration of free hormones in plasma. They can also interact with sex steroid-binding proteins and act as inhibitors of several steroid-metabolizing enzymes, thus playing a protective role against breast and colon cancers [14]. In the specific case of breast cancer, it has been suggested that secoisolariciresinol diglucoside (SDG) may play a protective role due to its ability to regulate the expression level of zinc transporters (zinc concentration is higher in breast cancer cells than in normal cells). In addition, one of the metabolites of SDG, enterolactone, would be able to suppress the proliferation, migration, and metastasis of cancer cells [41].

Specifically, lignans inhibit aromatase activity in adipose tissue of obese postmenopausal women. The result is evident in the reduction of circulating estrogen and serum levels of sex steroid hormones, which are implicated in the development of breast cancer [42].

Due to their antioxidant capabilities, lignans (particularly SDG) help reduce the risk of lupus nephritis, oxidative DNA damage, and lipid peroxidation, as well as prevent oxidative stress associated with metabolic syndrome [43].

A relevant activity of flaxseed (particularly its oil, rich in ALA, lignans, and fibers) is lowering cholesterol. Lignans, acting as selective estrogen receptor modulators, can reduce LDL levels (the “bad” cholesterol) and triglycerides and normalize HDL cholesterol in the blood [26]. In this way, flaxseed lignans highly reduce the risk of cardiovascular disease. In particular, SDG can prevent or delay the progression of atherosclerosis and thus prevent coronary artery disease, stroke, and peripheral arterial vascular disease [44].

Lignans also have antiglycemic activity, inhibiting the development of type 1 and type 2 diabetes by lowering the glycemic response in the blood [33]. Lignans’ antidiabetic activity is added to the influence of flaxseed fibers on insulin secretion and plasma glucose homeostasis. In fact, SDG reduces the concentration of C-reactive protein, which is related to insulin resistance in type 2 diabetes and glucosuria, so it may help reduce the incidence of type 1 diabetes and delay the development of type 2 diabetes in humans [43]. In addition, by prolonging satiety, lignans actively help reduce obesity [5].

Other recognized beneficial effects on human health include immunomodulatory activity, anti-leishmaniosis activity, inhibition of 5-lipoxygenase, and high efficiency in protection against rheumatoid arthritis. Since they can also bind to tubulins of the cytoskeleton, they can play an important antiviral action by interfering in the replication of viruses. In addition, they inhibit reverse transcriptase, so they are also effective in blocking the replication of RNA viruses [17].

Lignans can also have a role in reducing the symptoms of depression and stress: during these times, the human body produces pro-inflammatory cytokines (such as TNF- and IFN-) that cause mood swings. Lignans’ intake appears to promote the production of two polyunsaturated fatty acids-EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), which counteract such mood swings [1].

SDG has shown effects on mental stress. SDG administration to ovariectomized mice inhibited stress-induced behavioral changes and reversed the increase in serum corticosterone and adrenocorticotropic hormone levels induced by chronic stress [38]. Moreover, the effects of three flax cultivars with different lignan content were studied on postmenopausal women with vascular disease who showed signs of stress due to having to perform frustrating cognitive tasks. In these women, the intake of lignans significantly reduced blood pressure during the period of stress; in particular, the cultivar with the highest lignan content increased plasma fibrinogen levels much less than the others and reduced plasma cortisol levels more [45].

Given the strong binding of lignans to estrogen, their potential effect on the reproductive system has been studied and found to be influential. Although further studies are needed, in the meantime, attention should be paid to flaxseed consumption during pregnancy and lactation. Early results are comforting in that the intake of lignans during lactation reduced susceptibility to mammary carcinogenesis later in life, with no adverse effects on selective reproductive indices in mothers or offspring [43].

Despite the wealth of this information and the knowledge of so many mechanisms involving lignans, many studies are still necessary to answer still-unanswered questions (toxicity, bioavailability) and to better understand the role of lignans in health and disease prevention. In this way, it will be possible to develop adequate dietary guidelines and nutraceutical or pharmaceutical products capable of preventing cardiovascular disease and helping fight cancer [1]. To this end, it will be necessary to set up and optimize lignan extraction, purification, and analysis systems in order to have considerable quantities of pure lignans for in vitro and in vivo investigations and clinical studies [46].

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