



Lignan-Based Phytoestrogenic Nutraceuticals and Their Role in Human Health

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Abstract

Lignans are a distinctive class of phytoestrogenic polyphenol which occur extensively in the plant kingdom particularly in seeds, grains, vegetables and fruits. Over the last few years, scientists have developed increased interest in lignan since they possess diverse biological effects. Lignans would make good antioxidants and anti-inflammatories, heart protectors and may be useful in combating cancer. Transformation of the lignans found in plants to enterodiol and enterolactone which are mammalian enterolignans occurs by the activity of gut bacteria. This establishes a significant connection between food, intestinal health, and health. This paper gives a closer examination of the dietary lignans including their natural sources, molecular structure, metabolic pathways, rate of absorption and their role in the biological system. It emphasizes their role in preventing chronic illnesses, hormonal balance as well as in the interaction between the gut and the brain. According to scientific evidence, foods that are rich in lignans, including flax seed, sesame, rye, and whole grains are the indispensable elements of a diet that enhance the metabolic attributes and cardiovascular well-being. The review also covers recent innovations in extraction, the process methods and production of functional food stuffs.

Keywords: Lignans; Phytoestrogens; Gut Microbiota; Functional Foods; Antioxidant; Cardiovascular Health

Introduction

Polyphenols are a famous category of bioactive compounds in our food supply, which has been discovered to be of health benefit. The polyphenols, especially lignans, are unique and significant, and they have two phenylpropanoid units bonded by a 2-2 -bond [1]. The compounds exist in different parts of plants such as seeds, grains, fruits, vegetables, and beverages such as coffee and tea. Lately lignans have been in the limelight as they are capable of

being phytoestrogens. This implies that they are able to replicate or alter the action of estrogen through binding to estrogen receptors [2]. Gut bacteria are important to convert dietary lignans into enterodiol (ED) and enterolactone (EL) that affects our health. These substances also act as hormones, prevent damage, and decrease inflammation, which connects our diet and gut health to the general condition [3].

The lignan consumption across the globe differs widely depending on the food consumption. Enterolactone is more prevalent in the blood of those who consume large quantities of flaxed, rye and whole grains compared to those who consume processed grains [4]. This distinction reveals the effects of the diet concerning lignans intake and its advantages to health.

Evidence of increased lignan intake in various people and clinical environments has linked intake to reduced risk of heart disease, hormone-linked cancers, metabolic disorders and menopause symptoms [5]. Nevertheless, their ability to be absorbed by the body and how they are processed by individual gut bacteria are important issues that determine their efficacy. Consequently, awareness of the structure of lignans, their foods, body usage, and actions is important to enhance the prevention of diseases by our foods [6].

Lignan origins and categorization

Lignans are commonly present in a great number of plants. They act as defense and structural agents in plant cell walls. Dietary lignans tend to be categorized according to the nature of the chemical. These are secoisolariciresinol, matairesinol, pinoresinol, lariciresinol, syringaresinol and sesamin [7]. These substances may be free aglycones or glycosides coupled. The more common type is Glycosides which are predominant in most of the plants that we eat.

These sources are flaxseed (*Linum usitatissimum*) which contains the highest concentration among other foods. One hundred grams of it contains approximately 300 to 600 mg of secoisolariciresinol diglucoside (SDG) [8]. This is followed by sesame seeds (*Sesamum indicum*), which contain lignans such as sesamin and sesaminol, both of which are good antioxidants [9]. Whole-grain cereals, especially rye, wheat, oats, and barley, are significant sources of lignans in typical Western diets [10]. Other vegetables like broccoli, carrots, and kale, as well as fruits such as berries, apricots, and peaches, and legumes like lentils and soybeans, also provide lignans in smaller amounts that can still impact the body [11].

Biosynthesis

Lignans are produced by the phenylpropanoid biosynthetic pathway that belongs to the transformation of phenylalanine into cinnamic acid under the influence of phenylalanine ammonia-

lyase (PAL). Further enzymatic transformations of cinnamate-4-hydroxylase (C4H), and caffeic acid O-methyltransferase (COMT) result in the production of coniferyl alcohol, the major monolignol building block.

Oxidative coupling of two molecules of coniferyl alcohol by oxidases or peroxidases produces pinoresinol- the first real lignan. The additional reductions of the enzyme are catalyzed by pinoresinol-lariciresinol reductase (PLR) and secoisolariciresinol dehydrogenase (SDH) to produce secoisolariciresinol and then matairesinol. These intermediates can then be further subjected to other transformations to various lignans based on the plant species.

Therefore, lignan biosynthesis is one of the directions of the phenylpropanoid metabolism to the production of complex plant secondary metabolites having antioxidant and phytoestrogenic effects [15-17]. (Figure 1)

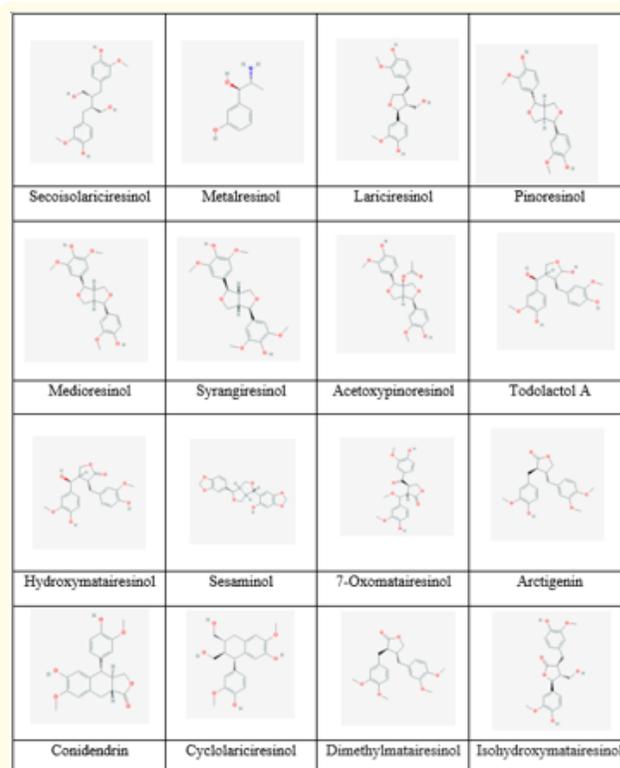


Figure 1: Some lignans structures.

Metabolism and bioavailability of lignan

Dietary lignans of flax seed, sesame and whole grains are not active in their plant form. The gut microbiota in the human intestine convert them into enterodiol and enterolactone, which are mammalian lignans. Such metabolites are then taken in the bloodstream and circulated in the body.

Their bioavailability is affected by their diet, the composition of the gut microbial population and the health of the intestines. Enterolignans are conjugated in the liver (to glucuronides and sulfates) and are excreted in urine or in bile. This process is efficient in different individuals, however, the constant consumption of lignan-rich foods would ensure the level of beneficial enterolignans is kept stable [18-21].

Factor Influencing lignan bioavailability

The absorption and metabolism of lignans are regulated by multiple nutritional and physiological factors:

- Nutritional content – Diets high in prebiotics and fiber feed microbial fermentation and enterolignan production [22].
- Gut microbiota diversity - humans with more diverse microbiome can convert SDG into EL [23].
- Food processing - Grinding and defatting flaxseed increases lignan extractability but high heat or oxidation may break down SDG [24].
- Women have more enterolactone in their blood and this can change with their periods or if they're taking hormones [25].
- Taking antibiotics can mess with your gut bacteria for a bit and really lower the amount of enterolignans in your blood [26].

How lignans support your body

They are antioxidants, anti-inflammatory and play with your hormones and metabolism. Here's the lowdown on how they work, based on studies. Fighting Inflammation and Oxidation Lignans clean up bad stuff called reactive oxygen species (ROS) in your cells and stop fats from breaking down [27]. They do this by sharing hydrogen which protects important stuff from damage and calms down free radicals. Lignans also mess with antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase [28]. In animal tests, SDG supplements increased

antioxidant enzymes in the liver and decreased oxidation markers like malondialdehyde [29]. Also, sesame stuff like sesamin and sesamol has been shown to reduce inflammation in blood vessels and liver by blocking COX-2 and NF- κ B pathways [30]. Keeping Your Heart Happy Studies show that eating more lignans or having more enterolactone in your blood is linked to lower heart disease [31]. It seems lignans help with fat processing, lower LDL oxidation and keep your blood vessels healthy. When people with high cholesterol took flaxseed for a few weeks, their LDL cholesterol dropped 10-15% and their good/bad cholesterol ratio improved [32]. Lignans also lower blood pressure by opening up blood vessels with nitric oxide and messing with angiotensin-converting enzyme activity [33]. Lignans can also help keep blood sugar stable by making insulin work better, reducing glucose production in the liver and managing fat cell hormones [34]. This means lignans could be helpful for preventing metabolic syndrome. Cancer Prevention and Hormone Balance Lignans act like estrogen because they bind to estrogen receptors (ER α and ER β). Depending on the amount of natural estrogen present they can act as estrogen or block it [35]. This may help with hormone related cancers like breast, prostate and endometrial cancer.

In a study of combined case control reports we found that women which had the greatest dietary intake of lignans had a 15 - 20% lower risk of developing post menopausal breast cancer as compared to those with the lowest intake [36]. Also we saw that high blood levels of enterolactone was associated with a reduced risk of prostate cancer and also less aggressive tumors [37]. As to the how it works, it includes the action of lowering estrogen production via inhibition of aromatase, changing estrogen receptor signaling, bringing about apoptosis, and reducing new blood vessel growth [38]. Also it is reported that lignans function as antioxidants which in turn protect DNA and decrease oxidative mutations.

Gut microbiome's role in immune regulation

Recent reports that present the relationship between lignans and gut microbiota as a two-way street. While it is the gut bacteria which play a key role in lignan activation what we also see is that lignans in turn play a role in shaping the microbiome's profile by promoting the growth of good bacteria like Bifidobacterium and Lactobacillus [39]. *In vitro* study also shows that lignans do a great job of increasing production of short chain fatty acids (SCFAs) in particular butyrate which in turn supports the health

of the mucosa and also has a role in modulating immune responses [40]. Also it comes out that enterolactone has anti-inflammatory action in intestinal cells by which it suppresses pro inflammatory cytokines like IL-6 and TNF- α [41]. From all of the above we see that lignans may play a role in the maintenance of gut homeostasis and in the prevention of metabolic and neurodegenerative diseases which have a base in chronic inflammation.

Benefits for brain and cognitive health

Lignans play a role in cognitive health and also have neuroprotective effects which we attribute to their action as antioxidants and estrogen mimics. Enterolactone is able to get past the blood brain barrier and changes the course of oxidative stress and neuroinflammation in neurons [42]. In animal models we see that which supplementing with SDG results in reduced amyloid-beta production and improved spatial memory [43]. In human beings, although the current information is minimal we have the trend which is the improving cognitive performance in adult human beings with a higher level of plasma enterolactone [44]. More studies are still needed to examine the problems of the lignan metabolism, the gut brain axis and neurodegeneration relationships.

Application of functional foods and their use

The interest has been growing on lignans and this has led to the research in its inclusion in functional foods, nutraceuticals and dietary supplements. However, we are able to note that there are issues that should be dealt with in the field of lignans stability, bioavailability, and palatability.

Extraction and processing techniques

Solvents such as ethanol and methanol that have been traditionally used in extraction are being replaced by green techniques such as the use of supercritical CO₂ extraction, ultrasound assisted extraction and enzymatic hydrolysis. Also these new techniques declare themselves to perform better regarding yield and bioactivity maintenance [45].

There is also a wide variation of the level of lignan found in food, depending upon the processing that has taken place. Depending on temperature, processes like milling, grinding and roasting can either make lignans more bioavailable to the body or degrade them [46]. An example is the fact that sesamin is more preserved in a light roast of sesame than in healthily roast sesame.

Preparing functional foods

The sourcing of lignan that has been most widely studied to be implemented in functional foods is Flaxseed. It has been added to yogurts, drinks, and baked foods successfully. Microencapsulation with alginate or maltodextrin are among the techniques employed to inhibit oxidative degradation of SDG and modulate its release into the intestines [47].

Recent work has considered the use of fermentation—by *Lactobacillus plantarum* or *Bifidobacterium longum*—to transform lignan precursors into enterolactone-like substances prior to consumption, enhancing the product's bioactivity [48]. That plant-based milk alternatives and energy bars contain lignans also suggests a very high chance of mainstream consumer acceptance.

Supplements and lignan-rich oils

Cold-pressed flaxseed oil and sesame oil continue to be the primary dietary sources of lipid-soluble lignans. For the purpose of regulating lipid levels, hormone balance, and alleviating menopausal symptoms, research has explored the use of supplements with pure SDG extracts [49]. Clinical validation and standardization of these products are still in their infancy, however.

Diet recommendations, tolerability, and safety

Overall, lignans are believed to be safe for consumption (GRAS) if the dose consumed is equivalent to the amount present in food. Ingestion of up to 500 mg/day of SDG or the equivalent from flaxseed [50] was not associated with any serious adverse effects.

There are a few things to keep in mind, though

- Because of their weak estrogenic activity, supplements at high doses can interfere with hormone treatments.
- Because of its mucilage and fiber content, it is significant to drink plenty of water when consuming flaxseed.
- It should be noted that certain individuals are susceptible to sesame product allergies.
- In spite of not having an officially established daily lignan intake recommendation, evidence from research points to a daily intake of 30 to 50 mg being beneficial. Foods that are high in sesame, flaxseed, and whole grains will assist you in doing this [8,9,10].

Conclusion

The lignans are a significant group of phytoestrogenic compounds that bring a connection between nutrition, metabolism, and disease prevention. Their ubiquity in widely eaten foods of plants has contributed to well-being in general as antioxidants, anti-inflammatory, cardioprotective and anticancer agents. One of the earliest characteristics of lignans is that they are metabolically transformed by intestinal microbiota into biologically active mammalian enterolignans, emphasizing the complexity of the interaction between dietary, gut-related and systemic metabolic and hormonal regulation. They have also extended their therapeutic and nutraceutical use due to advancement in methods of extraction, standardization procedures and formulations of functional foods. The research areas and suggestions involve further investigation of the gut microbiome-lignan interaction to gain a clear insight into inter-individual differences in enterolignan production and health outcomes. Extensive randomized trials that have a long-term duration are required to determine the optimum intake, bioavailability, and safety of various populations. Individual nutrition work (depending on the composition of microbiota and individual metabolic responsiveness) can be developed to improve the effectiveness of lignans. Also, new methods of delivery like nanoformulations and bio-enhanced functional foods may enhance stability and absorption. Another promising field of study is sustainable farming in order to add lignan content to the staple crops. Together, the inclusion of lignan supplemented foods containing flax, sesame, rye, and whole grains in a balanced diet is highly encouraged to promote cardiovascular, metabolic, and hormonal health and the role of this in preventive and therapeutic nutrition will be further developed by ongoing research.

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Conflicts of Interest

The authors have declared that they have no potential conflicts of interest.

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