ABSTRACT
Currently, there is a great focus on the relation between diet and degenerative diseases. Epidemiological studies have proved that lignan-rich diets help reduce risk of various hormone-dependent cancers, heart disease and osteoporosis. Lignans are another group of diphenolic compounds or phytoestrogens which are less investigated and are present in a wide variety of plants. Considering the health beneficial potential of food components, lignans are also becoming an interesting topic and consumption of lignan-rich foods are studied for their putative health beneficial effects on human health. Flaxseed is the richest plant source of lignans and omega-3 fatty acid (ALA). Secoisolariciresinol Diglucoside (SDG) is the principal and prospective bioactive lignan present in flaxseed. When ingested in relatively large amounts, it is converted to Secoisolariciresinol (SECO), which is further metabolized to the mammalian lignans enterodiol (ED) and enterolactone (EL) in the large bowel by the action of gut microflora. Additionally, SDG is effective in retarding the development of type II diabetes, which is associated with an increase in oxidative stress. SDG is a potent hypolipidemic agent due to its potential antioxidant activity. SDG is believed to play a crucial role in reducing the incidence of several diseases such as CVD’s, hypertension, cancers and inflammatory and autoimmune disorders. SDG and its metabolites were discovered to be potential non-synthetic antioxidant agents and possess anti-tumor, anti-mitotic, anti-diabetic, anti-cancerous, anti-lupus nephritis and weak estrogenic activities. Thus, they play a key role in human health. This review focuses on SDG as a potential therapeutic tool and its clinical significance.

Keywords: Phytoestrogen, Lignan, Secoisolariciresinol Diglucoside, Secoisolariciresinol, Enterodiol, Enterolactone.

INTRODUCTION:
Phytoestrogens are a diverse group of plant-derived compounds that structurally or functionally mimic mammalian estrogens and show potential benefits for human health. They have a chemical structure that is similar to that of estradiol. They may compete with estrogens for binding to estrogen receptors (ERs) and in doing so, may act as weak estrogen agonists or antagonists. Thus, phytoestrogens may act as antagonists in pre-menopausal women and replace endogenous estrogen in the post menopause. The level of endogenous estrogens reflects on estrogenic or antiestrogenic effect of phytoestrogens[1-3].
Phytoestrogens have been shown to have significant estrogen agonists/antagonists effect in animals and humans \(^4\). The adverse estrogenic effects of phytoestrogens on reproductive development have been observed in domestic and experimental animals. The type of estrogenic effect depends on both the relative potency of the compound and the time of exposure \(^3,5\). Additionally, phytoestrogens exert antioxidant, antitumor, anti-breast and prostate cancers, anti-diabetic, cardiovascular diseases, menopausal symptoms, osteoporosis and some other activities \(^4\)-\(^8\).

There are three major classes of phytoestrogens distributed in seeds, whole grains, berries, fruits, vegetables, nuts, broccoli and sprouts. These three classes of phytoestrogens, individually or in combination, are most likely the primary types of plant estrogens that deliver health benefits since other components are not provided in plant food diets in higher amounts \(^8\)-\(^11\).

**ACTION OF PHYTOESTROGENS IN THE BODY**

There are many different ways that phytoestrogens may work in the body. The chemical structure of phytoestrogens is similar to estrogen, and they may act as mimics (copies) of estrogen. On the other hand, phytoestrogens also have effects that are different from those of estrogen \(^3,8\). Phytoestrogens may either have the same effects as estrogen or block estrogen's effects depending on the dose of the phytoestrogen.

They act like estrogen at low doses but block estrogen at high doses \(^3,5\). Estrogen activates a family of proteins called estrogen receptors. Recent studies have shown that phytoestrogens interact more with some members of the estrogen receptor family, but more information is needed about how these receptors work, especially in breast cancer. Finally, phytoestrogens which act as estrogen mimics may affect the production and/or the breakdown of estrogen by the body, as well as the levels of estrogen carried in the bloodstream \(^9,11\).

Phytoestrogens which act differently from estrogen may affect communication pathways between cells prevent the formation of blood vessels to tumors or alter processes involved in the processing of DNA for cell multiplication. It is very possible that more than one of them may be working. Also, the effects in various parts of the body may be different \(^3,8\).

**CLASSIFICATION AND SOURCES**

There are three main classes of phytoestrogens namely isoflavones, coumestans, and lignans, which occur in either plants or their seeds. More than 300 foods have been shown to contain phytoestrogens.

**Isoflavones.**

Isoflavones are a type of phytoestrogens, or plant hormone that resembles human estrogen in chemical structure. By mimicking human estrogen at certain sites in the body, isoflavones provide many health benefits \(^12\).

The effects of the isoflavones are much less powerful than the estrogen hormones. In fact, the effectiveness represents around 1/1000 of the estrogen hormones. This is why isoflavones exercise a balancing effect when the level of estrogens is low, during the incidences like menopause. Isoflavones can also reduce the effect of the estrogen when the hormone levels are high, thereby reducing the risk of estrogen linked cancers \(^11\).

- **Sources:**
  Isoflavones are found in soybeans, chick peas and other legumes. However, soybeans are
unique because they have the highest concentration of these powerful compounds. Soy contains many individual isoflavones, but the most beneficial are genistein and daidzein.

The highest amounts of soy isoflavones are found in soy nuts and tempeh. Another natural source of isoflavones is red clover [9,13].

- **Chemical Structure:**
The chemical structure of isoflavones is very similar to that of our own estrogen. Because of this similarity in structure, they can interfere with the action of our own estrogen. **Figure 1** shows the chemical structure of the two most important isoflavones: daidzein and genistein [11, 12].

![Chemical structures of genistein and daidzein](image)

**Figure 1: Chemical structures of the two most important isoflavones: daidzein and genistein.**

**Coumestan.**
Coumestans are class of chemicals from plants that behave like estrogen in the body. They are thought to have a greater estrogenic activity than the isoflavones. Coumestans are the least studied of all phytoestrogens, but research has shown some cancer-preventing effects [14].

- **Sources:**
Coumestans are reported to be present in legumes such as, pinto beans, garbanzo beans, navy beans, kidney beans, lima black beans and black-eyed peas as well as in alfalfa trifolium species, clover trigonella and fenugreek. They are also found in honey bush tea and green rooibos tea (both African teas) [13].

- **Chemical Structure:**
The chemical structure of coumestan is resemble to that of our own estrogen **Figure 2** represents the structure of the most well-known coumestan (coumestrol) [3,14].

![Chemical structure of coumestrol](image)

**Figure 2: Chemical structure of the most well-known coumestan: coumestrol**

**Lignans**
Lignans are one of the three major classes of phytoestrogens. Plant lignans are polyphenolic substances which are derived from phenylalanine via dimerization of substituted cinnamic alcohols. Polyphenols are a family of organic compounds characterized by a wide range of biological activities. Among natural polyphenols, the products derived from shikimic and polyketide biogenic pathways, such as lignans, neolignans, cardanols and flavonoids are of special interest owing to their powerful antioxidant, antitumoral, antimitotic, antiviral, cardiovascular and immunosuppressive activities [10, 15].
**Sources:**
Several hundred lignans have been discovered in different parts of various plants, including wooden parts, roots, leaves, flowers, fruits and seeds. Wood knots in certain spruce and fir species constitute the richest known source of lignans in nature. Flax seed and sesame seed are among the highest known sources of lignans. The principal lignan precursor found in flaxseed is secoisolariciresinol diglucoside. Other sources of lignans include cereals (rye, wheat, oat and barley-rye being the richest source), pumpkin seeds, soybeans, broccoli, beans and some berries like the Schisandra chinensis. They are a group of phytonutrients which are found in seeds, grains and vegetables. Flaxseed is, by far the nature’s richest source of plant lignans (Table 1).

### Table 1: Sources of lignans[^10]

<table>
<thead>
<tr>
<th>Source</th>
<th>Amount per 100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flaxseed</td>
<td>300,000 µg</td>
</tr>
<tr>
<td>Sesame seed</td>
<td>29,000 µg</td>
</tr>
<tr>
<td>Brassica vegetables</td>
<td>185 - 2321 µg</td>
</tr>
<tr>
<td>Grains</td>
<td>7 - 764 µg</td>
</tr>
<tr>
<td>Red wine</td>
<td>91 µg</td>
</tr>
</tbody>
</table>

Secoisolariciresinol and matairesinol were the first plant lignans identified in foods. Pinoresinol and lariciresinol are more recently identified plant lignans that contribute substantially to the total dietary lignan intakes.

**Chemical Structure:**
Lignans are very complex class of plant compounds which have a role in the plant’s natural defense mechanism. They are phenyl propane dimers linked by ß-ß bonds with a 1, 4-diarylbutane structure (Figure 3). They are biosynthesized in the cell cytoplasm through action of enzymes of the phenyl propanoid pathway[^13,15].

![Figure 3: General structure of lignans](image)

**Classification of Lignans:**
The range of natural structures encountered is very diverse and can be exemplified with a proposed classification according to their skeleton to seven groups dibenzyl butanediols, tetrahydrofurans, furofurans, dibenzyl butyrolactones, tetralins, naphthalenes and dibenzo cyclooctadienes (Figure 4) [^5,10].
In spite of recognizing the distribution of lignans in plants, their biological purpose in nature is still unclear in most of the cases. It is however, known that the accumulation of lignans in the core of trees is important for the durability and longevity of the species.

- **Chemical Synthesis of Lignans:**
  Lignans have long been recognized as challenging targets for organic synthesis due to their complex and diverse architectures as well as their important pharmacological properties. To date, much effort has been concentrated on the synthesis of naturally occurring and biologically active compounds in their enantiomer-enriched form as in most cases the biological properties vary between the enantiomers \(^{[14,16]}\). The majority of approaches used in the synthesis of lignans are divided into four general groups. They are diastereoselective alkylation of chiral butyrolactones, diastereoselective conjugate addition to chiral 2-(5H)-furanones, routes involving cycloaddition reactions and routes involving the use of chiral oxazolidines.

**FLAX SEED**
Flaxseed also known as Linseed (*Linum usitatissimum L*), belongs to the family Linaceae \(^{[17]}\). Flax is grown for its value either as an oil crop or as a fiber crop, with fiber linen derived from the stem of fiber varieties and oil from the seed of linseed varieties \(^{[1,18]}\). It has gained recent attention as a potential functional food: since it is an exceptionally rich source of dietary lignan, possessing over 800-fold the amount in most other foods \(^{[19,20]}\). Canada is the world’s largest producer of flaxseed (about 38% of the total production), where it is grown annually on approximately 1.3 million hectares of land and harvested primarily for its seed oil \(^{[18,21]}\), then come China and India.

Flaxseed is the richest natural source of plant lignans, with secoisolariciresinol diglucoside. The concentrations of SDG in flaxseed vary with different cultivars. Eliasson et al. (2003) reported that SDG concentrations in twenty-seven flaxseed Species ranged from 1·19 to 2·59% for (+)-SDG and from 0·22 to 0·5% (w/w) for its diastereoisomer, (-)-SDG \(^{[22]}\). Additionally, flaxseed contains 35% of its mass as oil \(^{[23]}\), which contains unsaturated fatty acids like oleic acid (12–30%), linoleic acid (8–29%) and linolenic acid (35–67%) \(^{[17,23]}\).

- **Nutritional profile of whole flaxseeds:**
  Two (2tbs = 15 g of flaxseed) tablespoons provide the following naturally occurring fatty acids, lignin fiber, muilage and lignan.
It is known that SDG is the main and abundant lignan in flaxseed, it is reported by several studies that 15 g of flaxseed contains approximately 13.6 mg of lignan. The Table 2 below elucidated the proximate nutrients content of whole flaxseed.

Table 2: Nutritional profile of whole flaxseed (15g) [24, 25]

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha Linolenic Acid (Omega-3)</td>
<td>1,710 mg</td>
</tr>
<tr>
<td>Linoleic Acid (Omega-6)</td>
<td>480 mg</td>
</tr>
<tr>
<td>Oleic Acid (Omega-9)</td>
<td>540 mg</td>
</tr>
<tr>
<td>Lignin Fiber</td>
<td>1,003 mg</td>
</tr>
<tr>
<td>Mucilage</td>
<td>200.6 mg</td>
</tr>
<tr>
<td>Lignan</td>
<td>13.6 mg</td>
</tr>
</tbody>
</table>

- **Flaxseed as a nutraceutical and functional Food:**

Health professionals are recognizing the major roles that are being played by nutraceuticals in health enhancement. As a result, there is a dramatic increase in research aimed at identifying new functional foods and nutraceuticals ingredients from the natural sources.

Functional foods and nutraceuticals are becoming popular alternatives to pharmacological treatments by providing health benefits and/or reducing the risk of chronic diseases. Flaxseed is a rich source of three components with demonstrated cardio protective effects: dietary fiber, lignans (phytoestrogens) and the omega-3 fatty acid (alpha-linolenic acid) [26-28].

Dietary flaxseed may also offer protection against ischemic heart disease by improving vascular relaxation responses and by inhibiting the incidence of ventricular fibrillation [29]. Because of its high fiber content and laxative effect, flaxseed is also used to treat constipation and hemorrhoids, and appear to help hormone imbalances, such as those that cause menopausal symptoms [3, 13, 30].

Previous studies have reported the greater concentrations of enterolactone in milk of cows fed with whole flaxseed and flaxseed meal than those fed with the control diet. Those results suggest that feeding of whole flaxseed may result in changes in milk fatty acid composition and enterolactone content, which offer benefits for consumers and provide new information on the conversion of plant SDG from two flaxseed products into mammalian lignans in dairy cows [31].

Nutraceuticals document the potential for lignan consumption to inhibit serum cholesterol synthesis and reduce the incidence of diabetes (type I and II), atherosclerosis, coronary heart disease, and postmenopausal osteoporosis [32-34].

**SECOISOLARICRESINOL DIGLUCOSIDE (SDG)**

SDG is a plant lignan most notably found in flaxseed at levels of 0.6% to 1.8% and in much smaller amounts in flaxseed oil. It is classified as a phytoestrogen since it is a plant-derived, non-steroid compound that possesses estrogen-like activity [13, 13]. Flaxseed is the richest source of the lignan SDG as SDG oligomers, which are often after ingestion, hydrolyzed to break the ester linkages for the release of SDG and the glycosidic bonds for the release of SECO.

SECO is further metabolized to the mammalian lignans ED and subsequently converted to EL [33-38]. Farah et al. (2006) suggested that there is no significant difference between
SECO/SDG and BHT, suggesting flaxseed lignans may be good alternative antioxidant agents to minimize rancidity in oil-based food products [39].

SDG is present in enantiomeric forms with the (+) antipode in excess (about 99%) and the (-) antipode in minor concentration (about 1%). The existence of two SDG isomers was first reported by Bambagioti et al. (1994) [40, 41]. The molecular formula of SDG is C_{32}H_{46}O_{16} and its molecular weight is 686.3 daltons. The aglycone of SDG is also known as 2,3 - bis (3-methoxy-4-hydroxybenzyl) butane-1,4-diol. Figure 5 shows the chemical structures of SDG as well as SECO and their molecular weight.

![Figure 5: Structures of SDG and SECO](image)

SDG exists as a part of polymeric structure, in which it is covalently bound via ester linkages to 3-hydroxy-3-methyl glutaryl (HMG) as shown in Figure 6.

![Figure 6: Structures of SDG oligomer and HMG](image)

The flaxseed oligomer contains an average of three molecular of SDG and two molecular of HMG linked through an ester bond as demonstrated in Figure 7 [42, 43].

![Figure 7: Structure of flaxseed oligomer (average size, n=3)](image)
• Isolation of SDG

Around 20 patents on lignan and SDG extraction from flaxseed have been published in recent years starting from the mid of 1990s, most of them concerned mainly in different forms including SDG oligomer, SDG and SECO \[44,45\]. Several methods use a mixture of ethanol, methanol or some others chemical mixture as a solvent to extract SDG \[45\]. The extraction method takes advantage of the solubility of SDG in alcohol and water. The earliest report was in 1956 by Bake and Klosterman, using equal parts of 95% ethanol and 1, 4-dioxane \[46\].

An effective method for obtaining SDG purified lignan from extract of *Linum usitatissimum* seeds was proposed by Farah et al (2009) making the use of an aqueous ethanol with microwave irradiation. The obtained SDG was purified using column chromatography and its structure was conformed using IR, Mass, and NMR spectra \[45\]. The several patented methods used for obtaining SDG from flaxseed are summarized in Table 3.

Table 3: Summary of Patented Methods to Obtain SDG from Flaxseed \[45\]

<table>
<thead>
<tr>
<th>Inventor/date</th>
<th>Patent Type/Patent Number</th>
<th>Source</th>
<th>Interests</th>
<th>Method</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pizzey, G. R. 05/23/2006</td>
<td>United States Patent 20067048960</td>
<td>Flaxseed meal</td>
<td>Mechanical method for the production of high lignan flaxseed meal</td>
<td>Milling and sieving system using aspirator to separate lighter density portion (high in lignan) from coarser portion</td>
<td>Increasing the lignan content of processed flaxseed product by 3-7%</td>
<td>[47]</td>
</tr>
<tr>
<td>Westcott, N.D. Muir, A. D. (Saskatoon, CA) - 01/06/1998</td>
<td>United States Patent 5705618</td>
<td>Flaxseed meal</td>
<td>Chemical method for the extraction of SDG and cinnamic acid derivative</td>
<td>Mixtures of aliphatic alcohols including methanol, ethanol, isopropanol, or butanol with water, alcohol-to-water ratios ranging from 1.85:1 to 3:1; separating residual solids from the phenolic-rich alcohol solvent; base hydrolysis to liberate SDG and cinnamic acid derivatives from its oligomeric form</td>
<td>Up to 20 mg per gram of SDG (purity 90%)</td>
<td>[48]</td>
</tr>
<tr>
<td>Westcott, N.D. (Saskatoon, CA)</td>
<td>United States Patent 20016264853</td>
<td>Flaxseed meal</td>
<td>Chemical method for the extraction of SDG</td>
<td>Alcoholic extraction followed by ultrafiltration;</td>
<td>370 mg/g solids of SDG, 160 mg/g solids of</td>
<td>[49]</td>
</tr>
<tr>
<td>Patent holder</td>
<td>Date and location</td>
<td>Method/Process</td>
<td>Product/Outcome</td>
<td></td>
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</tr>
<tr>
<td>Paton, D.</td>
<td>07/24/2001</td>
<td>Oligomer/polymer</td>
<td>Low molecular weight species remain with a filtrate and higher molecular weight oligomer/polymer are retained on the ultrafiltration membrane. Cinnamic acid glucoside (measured as methyl ester), 50 mg/g solids of ferulic acid glucoside (measured as methyl ester) and 96 mg/g solids of HMGAG (measured as its dimethyl ester).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myllymäki, O.</td>
<td>08/27/2002</td>
<td>Whole flaxseed</td>
<td>Mechanical method for the production of fiber fraction rich in lignans. Removing flaxseed hull from flaxseed endosperm by abrasion, wherein a firstly removed outer portion of the husk is separated as a mucilage fraction and then a secondly removed inner portion is separated as a fibre fraction.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shukla, R.</td>
<td>07/27/2004</td>
<td>Plant materials including flaxseed</td>
<td>Chemical method for the production of the lignan complex. Removing cyanogenic sugars, reducing microbial component. Solvent extraction to obtain SDG polymer; ultrafiltration (while simultaneously adding solvent solution) to remove cyanogenic sugars and to reduce microbial content component. Lignan complex: 1.9 g/L (purity 11.8%); ultrafiltration: retentate (0.9 g/L) with 23.3% purity; permeate (0.2 g/L) with 8.1% purity.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobbins, T.</td>
<td>10/19/2004</td>
<td>Flaxseed meal</td>
<td>Chemical method for the extraction isolation, and purification of SDG. A continuous extraction method; solvent comprising acetone 45% acetone/55% water, solvent to feedstock ratio: 12:1 to 16:1 and water (35: 65 v/v) to extract SDG; separating residual solids. 19.3 grams of a lightcolored, fluffy hygroscopic solid containing 31% by wt. SDG with recovery of 90%.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name(s)</td>
<td>Country</td>
<td>Flax Product</td>
<td>Isolation Method</td>
<td>From the SDG-containing extract</td>
<td>Initial weight: 978 g of defatted flaxseed meal; SECO (18.2 mg/g):</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------</td>
<td>-------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Empie, M. (Forsyth, IL, US)</td>
<td>United States Patent 20056900240</td>
<td>Flaxseed meal other vegetable matter including soy tea, and cocoa</td>
<td>Chemical method for isolation of phytochemicals, including saponogenins and saponins, catechins, lignans, phenolic acids, and isoflavones</td>
<td>Ethanoic extraction; dissolving in water; ultrafiltration; freeze-drying</td>
<td>[52]</td>
<td></td>
</tr>
<tr>
<td>Gugger, E. (Latham, IL, US)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cui, W. (Guelph, CA) Han, N. F. (Brampton, CA)</td>
<td>United States Patent 20067022363</td>
<td>Flaxseed hulls and lignin rich flaxseed products for applications as ingredients for nutraceuticals, functional foods, feed and other food and nonfood products</td>
<td>Mechanical method using dehulling to obtain lignan rich flaxseed products</td>
<td>Continuous dehulling process, fractionation of the dehulled products, comparison with traditional extraction method with methanol: 1, 4 dioxane at 60°C for 36 hr.; centrifugation Supernatant hydrolysis with 0.5 M NaOH at room temperature for 24 h acidification of the hydrolyzate with 2M H2SO4 to pH 3 C 18 resin using water to remove sugars; eluting SDG with methanol</td>
<td>The SDG content in defatted flaxseed ranged from 0.9% to 3.0% by weight whereas in flaxseed hull, it was at least 10% percent by weight; It was found that the extraction efficiency of the lignan with alcohol was low, and the method was time consuming</td>
<td>[53]</td>
</tr>
<tr>
<td>Pihlava, J. (Rusko, FI) Hyvarinen, H. (Jokioinen, FI) Ryhanan, E. (Helsinki, FI) Hietanenemi, V. (Jokioinen, FI)</td>
<td>United States Patent 20040030108</td>
<td>Crushed flaxseed</td>
<td>Chemical method for the isolation of SDG</td>
<td>Supercritical carbon dioxide extraction 1-5 hours, pressure 300-450 atm and temperature 50-80°C alkaline hydrolysis (1M NaOH: MeOH, 1: 20 (w/v). to obtain SDG separation and purification with glass column chromatography using C18 as packing material</td>
<td>SDG with the particle size &lt;5 mm with 90% purity</td>
<td>[54]</td>
</tr>
<tr>
<td>Kankaanpaa</td>
<td>United States Patent 20040030108</td>
<td>Whole</td>
<td>Chemical</td>
<td>Cold and/or hot</td>
<td>Flax protein</td>
<td>[55]</td>
</tr>
</tbody>
</table>
- **Properties of SDG and SECO**

Earlier studies have estimated the physical properties of SDG as well as SECO in flaxseed, using several techniques such as \(^{1}H\) and \(^{13}C\) Nuclear Magnetic Resonance (NMR) and Electrospray – Mass Spectrometry (ES-MS). Table 4 represents the chemical formula of the major lignan in flaxseed, SDG and SECO along with some of their physical properties such as, molecular weight, melting point, and optical activity as measured and reported by many recent studies \(^{56-58}\).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>*Mol. Weight</th>
<th>Melting point (°C)</th>
<th>**Optical activity</th>
<th>(\alpha)_D</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R,R)-SDG</td>
<td>C(<em>{32})H(</em>{46})O(_{16})</td>
<td>687.7</td>
<td>118.0</td>
<td>-2.0°</td>
<td></td>
</tr>
<tr>
<td>(R,R)-SECO</td>
<td>C(<em>{20})H(</em>{26})O(_{6})</td>
<td>363.3</td>
<td>114.0</td>
<td>+37.0°</td>
<td></td>
</tr>
</tbody>
</table>

*MW was measured using ES-MS (+ve ion mode); **Ethanol was used for SECO and water was used for SDG.

- **Metabolism of SDG**

The lignans macromolecule act as a delivery system of SDG in the large intestine, where its metabolism take place by the action of microbial flora to give rise to the enterolignans. The Mammalian lignan ED with molecular weight of 302 and EL with molecular weight of 298 \(^{59}\) were identified in humans and animals by Setchell and others in 1980 \(^{60}\).

They are formed in the human body in the gastrointestinal (GI) tract, where GI bacteria hydrolyze the sugar moiety of SDG to release SECO \(^{61-65}\), after which it is bioactivated into enterolignans from the transverse colon onward. Single demethylation is a first step in the bioactivation, followed by dehydroxylation by the colonic microflora to give the mammalian lignan ED as represented in Figure 8. ED is presumed to be oxidized by the (GI) microbial flora to give EL. This may also be formed directly from matairesinol, although this is likely to be a minor metabolic route if other lignans are present in the diet \(^{66-68}\). Enterolignans concentration in urine are typically greater than in plasma, thus most analytical methods target the measurement of urinary lignan levels \(^{41}\).
It is believed that entrolignans may provide health benefits due to their weak estrogenic or anti-estrogenic effects, antioxidant activity, and inhibit the activity of certain enzymes, or by mechanisms yet unidentified. Human and animal studies identify the benefits of SDG consumption. SDG metabolites may protect against cardiovascular diseases (CVD) and the metabolic syndrome by reducing lipid and glucose concentrations, lowering blood pressure, and decreasing oxidative stress and inflammation. It may also reduce cancer risk by preventing pre-cancerous cellular changes and by reducing angiogenesis and metastasis [36].

- **Mechanism of action of SDG**

Non hormonal mechanism can be either as primary antioxidant (chain breaking) in which it reacts directly with lipid radicals and convert them into stable products, or as secondary antioxidants (preventive) in which it can lower the rate of oxidation by different mechanisms such as binding metal ions able to catalyze oxidative processes by scavenging oxygen, absorbing UV radiation, inhibiting enzymes or by decomposing hydro peroxides [3, 69].

The behavior of the lignans depend on the biological levels of estradiol. With regard to hormonal mechanism of lignans, at normal estradiol levels, the lignans act as estrogen antagonists, but in postmenopausal women (at low estradiol levels) they can act as weak estrogens [70, 71]. Other activities related to estrogen include the in vivo synthesis of 2-Hydroxyl estrogen, a compound that may protect against cancer [71] and inhibit the binding of estrogen and testosterone to receptors on sex hormone-binding globulin [72]. The presence of the oxidized metabolites is unique and may provide additional reasons for the health benefits of lignans. Classical antioxidant mechanisms show that the addition of an ortho hydroxyl group to a monophenol enhances the antioxidant activity of the original monophenol. Thus, some of the mammalian lignan metabolites may actually have greater or different activity than the parent lignan. Kitts and others (1999) reported that enterolactone and enterodiol had greater antioxidant activity than the parent [73, 74].
In *vitro* and *in vivo* studies suggest that flaxseed lignans (SDG) may have both non-hormonal (i.e. antioxidant) and hormonal, either agonists or antagonists (i.e. weak estrogenic / anti-estrogenic) effects [75-79] making them strong candidates for a role as natural cancer protective compounds [69,80]. There are substantial epidemiological investigations supports this hypothesis, because the highest levels of these lignans are found in food in countries or regions with low cancer incidence [69, 81].

- **Health benefits of SDG**

There is a considerable evidence suggest that SDG metabolites may provide health benefits due to their weak estrogenic or anti-estrogenic effects, antioxidant activity, ability to induce phase(2) proteins and/or inhibit the activity of certain enzymes, or by mechanisms yet unidentified.

SECO and SDG may possess chemopreventive properties in animals and humans [41,43,47,82], including the potential to protect against CVD and the metabolic syndrome. These possible potential effects are by reducing lipid and glucose concentrations, lowering blood pressure, and decreasing oxidative stress and inflammation [82-84]. Flax lignans may also reduce cancer risk by preventing pre-cancerous cellular changes and by reducing angiogenesis and metastasis [83-86].

SDG was found to prevent the development of diabetes type I and II [33, 87] and improve renal function in lupus nephritis [6]. Thus, dietary SDG has the potential to decrease the incidence of several chronic diseases that result in significant morbidity and mortality in industrialized countries. The available literature makes it difficult to clearly identify health effects of SDG because of the wide variability in study methods. However, the current evidence suggests that a dose of at least 500 mg SDG/day for approximately 8 weeks is needed to observe positive effects on cardiovascular risk factors in human patients [82].

Now a days, it has become a challenging for food industries to produce food products that are convenient, fresh, and offer health benefits in addition to their nutritional qualities. Thus, flaxseed and its lignan extracts appear to be safe for most adult populations. Flaxseed is a functional food due to its health benefits according to Health Canada, though animal studies suggest that pregnant women should limit their exposure [45].

Various studies are mainly focusing on individual flax components to discover and conform their health benefits and mechanism of action. **Table 5** represents the proposed health benefits of the flaxseed lignan SDG, which play a magnitude role in disease prevention and health promotion.
### Table 5: The proposed health benefits of SDG

<table>
<thead>
<tr>
<th>Lignan</th>
<th>Proposed Health Benefits</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDG</td>
<td>1. Treatment of benign prostate hyperplasia.</td>
<td>[86,104,105]</td>
</tr>
<tr>
<td></td>
<td>4. Reduces risk of cardiovascular disease, inflammatory bowel disease, rheumatoid arthritis.</td>
<td>[23,29,84,94]</td>
</tr>
<tr>
<td></td>
<td>5. Anti-diabetic compound.</td>
<td>[5,33,87]</td>
</tr>
<tr>
<td></td>
<td>6. Anti-tumorigenic effect on certain cancers.</td>
<td>[73,86,96,98]</td>
</tr>
<tr>
<td></td>
<td>7. Cholesterol-lowering effects.</td>
<td>[72,83,84,94]</td>
</tr>
</tbody>
</table>

- **Biological Potencies of SDG**

SDG is a potential multifarious bioactive phytoestrogen. Various biological potencies of SDG are often attributed to its conversion to the mammalian lignans ED and EL. However, intermediate compounds generated during the digestion and metabolism of SDG and its aglycones and SECO, may also be the principal bioactive molecules.

The first interest in biological activity of SDG arose in the early 1980s when investigators reported that the level of lignans in the body were lower in patients with breast cancer than in patients free of tumors. It was also noted that vegetarians had higher concentrations of lignan substances than non-vegetarians [88,89].

- **Antioxidant Properties:**

Free radicals are responsible for aging and causing various human diseases. A study has shown that antioxidant substances which scavenge free radicals play a crucial role in the prevention of free radical-induced diseases, by donating hydrogen radicals [74]. The primary radicals are reduced to non-radical chemical compounds and are then converted to oxidize antioxidant radical [90,91].

Lignans can act as platelet-activating factor-receptor antagonists, and inhibit the production of oxygen free radicals by neutrophils [92-94]. SDG, a phytoestrogen of flaxseed, has been found to possess antioxidant properties [93,95].

The antioxidant activities of the flaxseed lignan SDG and its mammalian lignan metabolites, ED and EL, were evaluated in both lipid and aqueous in vitro model systems [73]. All the three lignans significantly inhibited the linoleic acid peroxidation at both 10 and 100 µM over a 24-48 h of incubation at 40 °C. The efficacy of SDG and particularly the mammalian lignans ED and EL to act as antioxidants in lipid and aqueous in vitro model systems, at relatively low concentrations (i.e. 100 µM), potentially achievable in vivo, is an evidence of a potential anticarcinogenic mechanism of flaxseed lignan SDG and its mammalian metabolites ED and EL [74,95]. An early study has shown that SDG and its metabolites are their scavenger of ·OH and the effectiveness of these compounds in some of the diseases like cancer could be due to their antioxidant activity [34].
Generally, one phenol group on the lignans is oxidized, suggesting that the number of phenols per molecule may not predict radical scavenging antioxidant ability of lignans. Therefore, the antioxidant is highest with SECO and ED and lowest with SDG, and it may be that the additional alcohol oxidation pathway contributes to its greater antioxidant ability \cite{94,95}. Therefore, on prevention of lipid oxidation the best alternative of BHT will be SECO \cite{93}.

**Antitumor Properties:**
Previous studies have shown that dietary flaxseed supplementation with SDG can reduce the growth of established human breast tumors in athymic mice with low circulating estrogen concentrations \cite{96}, regardless of dose, appeared to delay the progression of N-methyl-N-nitrosourea (MNU)-induced mammary tumorigenesis \cite{97}. SDG significantly reduces pulmonary metastasis of melanoma cells and inhibits the growth of metastatic tumors which may form in the lungs \cite{97,98}.

There is considerable evidence from epidemiological studies correlating high concentrations of lignans in the body fluids with a low incidence of hormone-dependent tumors \cite{96}. In addition, lignans are found to be growth inhibitors of colon tumor cells and they may act through mechanism(s) other than anti-estrogenic activity \cite{95}, particularly SDG has an antitumor effect when provided at the early promotion stage of tumorigenesis \cite{83}.

**Anti-Inflammatory Properties:**
Many researchers have found that flaxseed lignans (SDG) reduce renal inflammation in all animals and lipid peroxides in polycystic kidney disease (PKD) females \cite{99}. A strong interaction between SDG and flaxseed oil (FO) is observed in renal fatty acid (FA) composition of female kidneys only, suggesting increased conversion of C₁₈ PUFA to C₂₀ PUFA. SDG reduced renal release of PGE₂ in both genders. Gender influences the effects of flaxseed derivatives in Han: SPRD-cy rats. Gender-based responses to environmental factors, such as dietary lipid sources and micronutrients, may contribute to gender-based differences in disease progression rates \cite{99}.

**Anti-Diabetic Properties:**
Reactive oxygen species (ROS) implicate in the development of diabetes mellitus. An investigation was made on the effects of SDG on the development of diabetes in rats, to determine if SDG can prevent/reduce the development of diabetes and if this prevention/reduction is associated with reduction in oxidative stress \cite{32,87}.

SDG is believed to prevent the development of diabetes type I [insulin dependent diabetes mellitus (IDDM)] by approximately 71% \cite{32}. This prevention was associated with a decrease in serum and pancreatic- malondialdehyde (MDA) and an increase in antioxidant reserve. These findings suggest that IDDM is mediated through oxidative stress. Hypoglycemic effect of SDG in type-II diabetes is also reported. This effect could be due to an increase in the expression of phosphoenolpyruvate carboxykinase (PEPCK), a rate-limiting enzyme in the gluconeogenesis in the liver. It is possible that the hypoglycemic effect of SDG in type-II diabetes is due to suppression of expression of PEPCK gene \cite{87}.

**Antimicrobial properties:**
Several studies have shown that lignans are good antibacterial plant extracts. Jun *et al.* found that lignans have both in *vivo* and in *vitro* antifungal activity in their demonstration \cite{100}. Lignans also showed antimicrobial activity of different selectivity and different MICs for
each microorganism \(^{[101]}\), SDG is also found to have potential anti-bacterial activity against microbial pathogens \(^{[102]}\). The antibacterial effect of SDG against clinically important pathogenic bacteria can be a preferred supplement to its known health benefits as antibacterial agents and usage in food system.

**Anti-Cancer Properties:**
There are epidemiological, laboratory and clinical evidences which indicate that phytoestrogens have anti-cancer effect on the breast \(^{[84]}\) and prostate \(^{[104]}\). Lignans with phytoestrogenic properties are abundant in flax seed. When ingested in relatively large amounts, phytoestrogens have been shown to have significant estrogen modulating effects in animals and humans \(^{[4]}\).

Flaxseed meal (FM) containing (5% or 10%) was found to reduce the epithelial cell proliferation by 38.8-55.4% and nuclear aberrations by 58.8-65.9% in female rat mammary gland \(^{[91]}\). These protective effects were accompanied by increases in urinary lignan excretion indicating that they may be related to the ability of flaxseed to provide lignan precursors. Dietary flaxseed may be chemopreventive for intestinal tumor development in Apc (Min) mice possibly by increasing omega -3 fatty acid levels, lignans, and decreasing Cyclooxygenase-1 and Cyclooxygenase-2 levels \(^{[105]}\).

**Effect of SDG in Breast Cancer:**
Incidence of hormone dependent cancers such as breast cancer is higher in Western countries than in Asian countries. There are substantial research findings that document the benefits of lignans for breast health. The binding affinity of lignans is higher to the estrogen receptor. The structure of flaxseed lignans, are similar to that of endogenous sex steroid hormones thus, it acts in vivo to alter hormone metabolism and reduce subsequent cancer risk in postmenopausal women \(^{[84]}\). In human objects, the influence of flaxseed and its lignans on breast health in postmenopausal women was examined. The study in Eastern Finland, where dietary lignan intake is typically above that of women in the U.S. found that higher blood concentrations of SDG that resulted in significant reduction in breast cancer risk \(^{[85,91]}\).

Another study noted that, the highest phytoestrogen consumption and concentrations in biological fluids are seen in countries where cancer incidence is low. The lowest concentrations of phytoestrogens were found in breast cancer patients or in women at high risk for breast cancer. These findings led researchers to investigate the effects of the SDG found in flax and mammalian lignans for its protective effects in animals. The animals were given a flaxseed supplement along with a carcinogen and a high fat diet. The result was a highly significant reduction in size and number of breast tumors \(^{[85]}\). This anticarcinogenic potency could be due to antioxidant effects or inhibition of aromatase, inhibition of protein tyrosine kinases competition with estradiol for the nuclear type II estrogen binding site inhibition of angiogenesis and/or stimulation of SHGB synthesis.

Flaxseed lignans (SDG) are associated with reduced risks of estrogen and progesterone positive postmenopausal breast cancer in a Western population which does not consume a diet rich in soy, and associated with a decrease risk of lung cancer \(^{[31]}\). Specifically, high intake of the lignans ED and EL, and use of hormone therapy were associated with a 50% reduction in risk of lung cancer. Confirmation of these findings is still required in large-scale and hypothesis-driven prospective studies \(^{[7]}\).
Effect of SDG in Prostate Cancer:

There are numerous reports on the potential tumour suppressive influence of lignans. Previous studies have shown that, Asian men have much lower incidences of prostate cancer and possibly of benign prostatic hyperplasia (BPH) than their Western counterparts. Vegetarian men also have a lower incidence of prostate cancer than omnivorous males, beside estrogenic activity, flaxseed can interfere with steroid metabolism and bioavailability, and also inhibit enzymes, such as tyrosine kinase and topoisomerase, which are crucial to cellular proliferation and hence may contribute to lower incidences of prostate cancer without affecting sex hormone levels. A case-control study conducted in Scotland found that higher serum enterolactone concentrations were associated with a lower risk of prostate cancer.

SDG has shown over the short term to decrease some early markers of colon cancer risk. In this study, colon cancer protective effect of flaxseed is due to SDG which is associated with increased beta-glucuronidase activity. Anneleen et al. (2008) have reported, beta-glucuronidase activity may play a beneficial role in their presence by increasing mammalian lignan absorption and enterohepatic circulation.

Plasma enterodiol and enterolactone were not associated with risk of colorectal cancer after adjustment for known colorectal cancer risk factors. These findings do not support the hypothesis that high plasma enterodiol or enterolactone concentrations are associated with reduced risk of colorectal cancer, and they may have a therapeutic role in lupus nephritis.

Cardiovascular Enhancing Properties:

Multiple clinical dietary intervention trials report that consuming flaxseed daily can modestly reduce circulating total cholesterol (TC) by 6-11% and low-density lipoprotein (LDL) cholesterol by 9-18% in normolipemic humans. Reduction of TC by 5 - 17% and 4-10% of LDL cholesterol in hypercholesterolemic patients, as well as lower various markers associated with atherosclerotic cardiovascular disease in humans. It is reported that the dietary fiber and/or lignan content of flaxseed provides the hypocholesterolemic action.

Flaxseed and SDG have been reported to reduce serum lipids and the extent of hypercholesterolemic atherosclerosis and this effect is associated with a decrease in serum cholesterol, LDL-C, and lipid peroxidation product and an increase in HDL-C and antioxidant reserve. Pattanaik et al. have reported that dietary flaxseed lignan extract decreased plasma cholesterol and glucose concentrations in a dose-dependent manner, and it slows the progression of atherosclerosis but have no effect on regression of atherosclerosis. Suppression of atherosclerosis by flaxseed is the result of its lignan content and not the result of ALA content.

Martin et al. found that flaxseed contains lignans with antioxidant activities and inhibit platelet-activating factor (PAF). Pretreatment with flaxseed attenuated endotoxin-induced cardiac dysfunction and cellular damage and prevent hypercholesterolemia-related heart attack and strokes.

CONCLUSION

The present review provides a better understanding of the SDG a principal lignan of flaxseed, and its metabolites, mammalian lignans which are produced by the action of gut microflora. The present review includes studies that report the SDG used which was extracted from...
different fractions that obtained upon dehulling of flaxseeds. SDG is known for its prospective antitumor, antimitotic, anticancer (breast, colon and prostate), antioxidant potencies and weak estrogenic activity. Lignans may act as antagonists in pre-menopausal women and replace endogenous estrogen in the post menopause. This property has already been in use in the hormone replacement therapy. Thus, herbal remedies with flaxseed-based ingredients have become popular in recent years instead of the conventional therapy with estrogen.

SDG provide a stimulating effect on breast cancer cell growth at low doses and inhibit tumour cell proliferation at higher doses. Being a potent natural antioxidant, it is found to reduce the development of diabetes by 75% and inhibits platelet-activating factor (PAF). SDG was suggested to be used as a good source of natural antioxidant similar to BHT. This aspect is also supported by our results with regard to the dose-dependent effect of SDG from different fractions of flaxseed extracts. Added to these, there are no any known side effects or toxicity of lignan usage although they are considered to have fewer side effects due to their natural origin. However, sufficient data about dosages and long-term studies are still missing.

SDG also showed antimicrobial activity of different selectivity and different MICs for each microorganism, and also found to have both in *vivo* and in *vitro* antifungal activity. SDG is also found to have potential anti-bacterial activity against microbial pathogens. The antibacterial effect of SDG against clinically important pathogenic bacteria can be a preferred supplement to its known health benefits as antibacterial agents.

SDG from flaxseed can be further extended to exploit its possible application for various health benefits as nutraceuticals and food ingredient. However, more research is needed in this direction before we can elucidate whether or not SDG supplementation protects against disease in humans. These studies may support the use of the multifarious bioactive compound (SDG) in several ways all over the world and encourage the researcher for further investigations.

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