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Review Article

SECOISOLARICIRESINOL DIGLUCOSIDE - A POTENTIAL BIOMEDICINE OF LINUM USITATISSIMUM

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ABSTRACT

Lignans are a group of diphenolic compounds or phytoestrogens which are present in a wide variety of plants however less investigated. Plant lignans are phenolic compounds generally containing a dibenzylbutane structure. 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 recognized health beneficial effects on human health. Secoisolariciresinol Diglucoside or SDG is the major lignin found in flaxseed with apparent health aids. It belongs to the phenolic chemical group. SDG and its metabolites are gaining attention due to their abundant health aids like anti antioxidant, anti-hyperglycemic and anticancer properties. SDG is believed to play a crucial role in reducing the incidence of several diseases such as hypertension, cardio vascular diseases, cancers and inflammatory diseases. Studies have proved that the lignan rich diets help to reduce the risk of various cancers and heart diseases. This review article elucidates the role of SDG as a biomedicine and also the safety aspects. Although, substantial research activities especially the clinical and pharmacokinetic studies in humans are prerequisite to validate these possessions.

Keywords: Lignan; SDG, Secoisolariciresinol diglucoside; Flax seed

1. INTRODUCTION

Linum usitatissimum also known as common flaxseed or line seed. SDG is an antioxidant, phytoestrogen presented in flax, sunflower, sesame and pumpkin seeds. Among these seeds, flaxseeds are by far the nature's richest source of plant lignans (Table1) [1].

SDG is a precursor of mammalian lignans [2, 3] which are produced in the colon from chemicals in foods. SDG is the major lignan found in flaxseed [4, 5], approximately 13.6 mg of lignan presented in 15 g of flaxseed [6, 7]. 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 [8, 9] SDG known to have antioxidant [10], anti-hyperglycemic [11, 12] and anticancer properties [13].

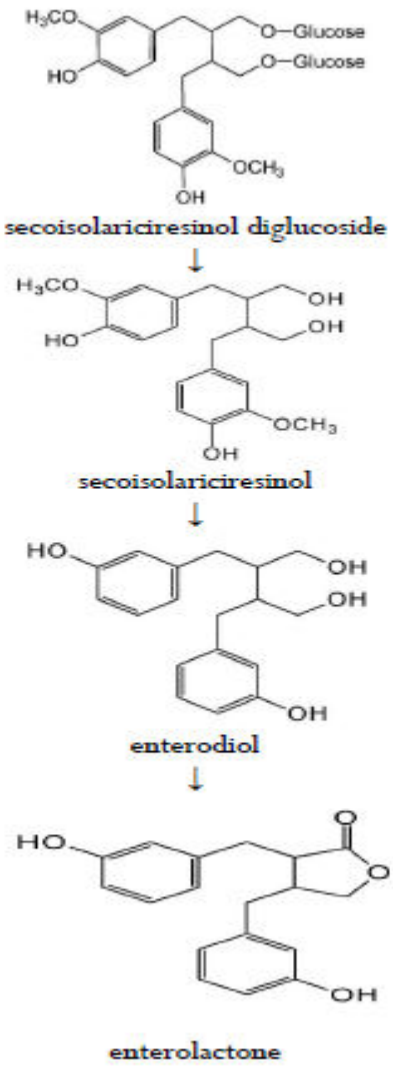
SDG is believed to play a crucial role in reducing the incidence of several diseases such as hypertension, cardio vascular diseases, cancers and inflammatory diseases [14-18]. SDG once ingested, will converted into the active mammalian lignans enterodiol (ED) and entero-lactone (EL) in the colon by intestinal bacteria [19-21].

Table 1: Lignan content (mg/100 g) of seeds

Product/ Seeds	Total Lignan (mg/100 g)
Flaxseed (Linum usitatissimum L.)	301 129
Sesame seed (Sesanum indicum L.)	39 348
Sunflower seed (Helianthus annuus L.)	891
Cashew (Anacardium occidentale L.)	629
Peanut (Arachis hypogaea L.)	94
Poppy seed (Papaver somniferum L.)	10

SDG at first undergoes hydrolysis to yield the aglycone plant lignan secoisolariciresinol (SECO). SECO afterwards converted to enterodiol (ED) and enterolactone (EL), first by dehydroxylation and demethylation to yield ED, which can then be oxidized to form EL (Fig 1) [22].

Defatted linseed and SDG, improved heart and liver constitution but not whole seed, decreased fat vacuoles in liver and decreased plasma leptin concentrations. Various results are showing that the individual components of flaxseed produce greater potential therapeutic responses in rats with metabolic syndrome than whole linseed [23].



The purpose of the present review is to provide a summary of recent advances regarding the potential health benefits of the flax lignan SDG and also the safety aspects of SDG. More in-vivo studies are needed to ascertain the propitious effects of lignans secoisolariciresinol and to see if there are any dangers in possible overdoses.

2. ISOLATION OF SDG FROM LINUM USITATISSIMUM:

The initial workers who reported a laboratory process for extracting SDG from defatted flaxseed (meal) were Bakke and Klosterman (1956) by using equal parts of 95% ethanol and 1,4-dioxane [24].

An efficient 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. A variety of organic solvents including methanol, ethanol, 1,4-dioxane, acetone, isopropanol, butanol or mixtures are used [25]. Table 2 shows different extraction methods used for SDG isolation from flaxseed.

3. BIOLOGICAL SIGNIFICANCE OF SDG

3.1. Antioxidant activity

SDG has a high antioxidant potential and may serve as a good source for anticancer and other degenerative diseases [36] by increasing the activities of hepatic antioxidant enzymes like, CAT, POX, and SOD, which in turn protects the vital organs against xenobiotic and other damages and decreased MDA levels in livers and kidneys of CCL_4-induced rats. SDG was proven to be more effective antioxidant than ED and EL against 1,1-diphenyl-2-picrylhydrazyl (DPPH), and 2,2′-azo-bis(2-amidinopropane) dihydrochloride (AAPH)-initiated peroxyl radical plasmid DNA damage and phosphatidylcholine liposome lipid peroxidation [37]. Flaxseed lignans SDG, SECO, ED and EL are found to be equal or somewhat more potent than BHT and vitamin E. Flaxseed lignans could be a good choice in terms of natural antioxidants with oil stability [38]. Furthermore, a recent study comparing flaxseed oil and flaxseed lignan showed that SDG could prevent oxidative stress related with metabolic syndrome [39]. SDG also scavenged radiation-induced HOCl in physiological solutions, and a synthetic SDG was suggested as a promising attenuator of oxidative stress-induced inflammatory tissue damage [40].

3.2. Anti-Hyperglycemic activity

SDG exhibits anti hyperglycemic effect by preventing the liver from peroxidation damage through inhibition of ROS level mediated increased level of enzymatic and non-enzymatic antioxidants. And, also in maintaining the tissue functions which results in improving the sensitivity and response of target cells in STZ-induced diabetic rats to insulin [41]. SDG reduces C-reactive protein concentrations which are associated with insulin resistance and diabetes mellitus in type 2 diabetics [42]. Apart from flaxseed fibers studies have shown that SDG-containing nutrients also affect plasma glucose homeostasis [43]. SDG was also shown to setback the development of diabetes in Zucker fatty rat type 2 diabetes model, which was coupled with reduction of serum MDA and glycated hemoglobin (A1C) levels [44].

Inventor/date	Patent type/patent number	Source	Interests	Method	Results
Pizzey, G. R. 05/23/2006	United States Patent 20067048960 [26].	Flaxseed meal	Mechanical method for the production of high lignan flaxseed meal	Milling and seiving system using aspirator to separate lighter density portion (high in lignan) from coarser portion	Increasing the lignin content of processed flaxseed product by 3-7%
Westcott, N.D. Muir, A. D. (Saskatoon, CA) - 01/06/1998	United States Patent 5705618 [27].	Flaxseed meal	Chemical method for the extraction of SDG and cinnamic acid derivative	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	Up to 20 mg per gram of SDG (purity 90%)
Westcott, N.D. (Saskatoon, CA) Paton, D. (Saskatoon, CA) - 07/24/2001	United States Patent 20016264853 [28].	Flaxseed meal	Chemical method for the extraction of SDG oligomer/ polymer	Alcoholic extraction followed by ultrafiltration; low molecular weight species remain with a filtrate and higher molecular weight oligomer/polymer are retained on the ultrafiltration membrane	370 mg/g solids of SDG, 160 mg/g solids of 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 HMGA (measured as its dimethyl ester)
Myllymäki,O. (Espoo, FI) - 08/27/2002	United States Patent 20026440479 [29].	Whole flaxseed	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	800-1480 mg/100g of total lignans
Shukla, R. (Decatur, IL)	United States Patent	Plant materials	Chemical method for the production	Solvent extraction to obtain SDG polymer;	Lignan complex : 1.9 g/L (purity

Hilaly, A. K. (Springfield, IL) Moore, K.M. (Mount Zion, IL) - 07/27/2004	20046767565 [30].	including flaxseed	of the lignin complex; removing cyanogenic sugars; reducing microbial component	ultrafiltration (while simultaneously adding solvent solution) to remove cyanogenic sugars and to reduce microbial content component	11.8%); ultrafiltration: retentate (0.9 g/L) with 23.3% purity; permeate (0.2 g/L) with 8.1% purity
Dobbins, Thomas A. (Howard, OH) Wiley, David B. (Warsaw, OH) - 10/19/2004	United States Patent 20046806356 [31].	Flaxseed meal	Chemical method for the extraction, isolation, and purification of SDG	A continues extraction method; solvent comprising acetone 45% acetone/55% water, solvent to feedstock ratio: 12:1 to 16:1and water (35: 65 v/v) to extract SDG; separating residual solids from the SDG-containing extract	19.3 grams of a lightcolored, fluffy hygroscopic solid containing 31% by wt. SDG with recovery of 90%
Empie, M. (Forsyth, IL, US) Gugger, E. (Latham, IL, US) - 05/31/2005	United States Patent 20056900240 [32].	Flaxseed meal; other vegetable matter including soy, tea, and cocoa	Chemical method for isolation of phytochemicalsincluding saponogenins and saponins, catechins, lignans, phenolic acids, and isoflavones	Ethanolic extraction; dissolving in water; ultrafiltration; freeze-drying	Initial weight: 978 g of defatted flaxseed meal; SECO(18.2 mg/g)
Cui, W. (Guelph, CA) Han, N. F. (Brampton, CA) - 04/04/2006	United States Patent 20067022363 [33].	Flaxseed hulls and lignanrich flaxseed products for applications as ingredients for nutraceutic als, functional foods, feeds and other food and non food products	Mechanical method using dehulling to obtain lignan rich flaxseed products	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 for24 h; acidification of the hydrolyzate with 2M H2 SO4 to pH 3;C 18 resin using water to remove sugars; eluting SDG with methanol	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
Pihlava, J. (Rusko, FI) Hyvarinen, H. (Jokioinen, FI)	United States Patent 20040030108 [34].	Crushed flaxseed	Chemical method for the isolation of SDG	Supercritical carbon dioxide extraction 1-5 hours, pressure 300-450 atm and temperature 50-	SDG with the particle size <5 mm with 90% purity

Ryhanen, E. (Helsinki, FI) Hietantemi, V. (Jokioinen, FI) - 02/12/2004				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	
Kankaanpaa-Anttila, B. Anttila, M. 1999	United States Patent 5925401 [35].	Whole flaxseed	Chemical method for producing a product containing flax proteins and flax mucilage	Cold and/or hot pressed to separate oil; alkaline extraction followed by acid precipitation	Flax protein product containing flax mucilage

3.3. Anti-Hypertensive activity

Studies indicated that flaxseed lignan supplements have beneficial associations with C-reactive protein and also suggest that lignans have possible lipid and blood pressure-lowering associations [45]. SDG is a long-acting hypotensive agent, and the hypotensive effect is mediated through the guanylate cyclase enzyme [46]. Smaller doses of SDG produced, dose-dependent decreases in the systolic, diastolic, and mean arterial pressures, heart rate remained unchanged.SDG decreased angiotensin I-induced rise in the systolic, diastolic, and mean arterial pressures by 60, 58, and 51%, respectively, at 15 minutes and 48, 46, and 30%, respectively, and at 60 minutes, a potent ACE inhibitor [47].

3.4. Cardiovascular Health

Studies indicating high fat diet containing SDG reduces liver triglycerides content, serum triglycerides, total cholesterol, insulin and leptin concentrations and also resulted in significantly reduced visceral fat gain when compared to the high fat diet without SDG [48]. SDG consumption may safeguard against the development of chronic diseases, such as cardiovascular diseases [17, 49]. The studies proved the effects of SDG and its metabolites in mediating the serum total cholesterol, low density lipoprotein, total cholesterol and high density lipoprotein ratios which reduced the occurrence of androgenic complications and also effected antioxidative prevention [50]. SDG proved as a probable cardiovascular protector by mediating the metabolism of total cholesterol, LDL-cholesterol, HDL-cholesterol, triacylglycerides and glucose metabolism in some human studies. Dietary flaxseed lignan extract shows the decreased plasma cholesterol and glucose concentrations in a dose-dependent manner [51]. A recent study on the potential protective effects of SDG in monocrotaline-induced pulmonary arterial hypertension on male rats reveals that SDG pretreatment decreased right ventricular hypertrophy, reactive oxygen species (ROS) levels, lipid peroxidation, catalase, superoxide dismutase, glutathione peroxidase activities, alanine transaminase (ALT), and aspartate transaminase (AST) plasma levels, compared to those in the monocrotaline group [52].

3.5. Anti-cancer activity

The significant role of SDG against some cancers (breast, lung and colon) as a result of its strong anti-proliferative, antioxidant activity has been established in animal and human studies. SDG and lignan supplementation in rat's diet resulted in aberrant crypts showing the anticancer role of these molecules [53]. Pretreatment of SDG decreases the risk of colon carcinogenesis, with reduced total number of aberrant crypts and foci significantly by 41-53% and 48-57% respectively [54-55]. In this study, colon cancer protective effect of flaxseed is due to SDG which is associated with increased beta-glucuronidase activity. The sequence of studies have shown that progression of N-methyl-N-nitrosourea-induced mammary tumorigenesis results in development of carcinogenesis and SDG has proven to delay the progression of this phenomenon by regulating the terminal end bud differentiation [56]. Role of SDG is in mediation of Zn concentration which observed more in breast cancer tissue compared to tissue of normal breast which may provide protection against breast cancer by limiting angiogenesis in such cases [57].

In addition, SDG was considered a chemopreventive agent against malignant mesothelioma owing to its ability to reduce acute asbestos-induced peritoneal inflammation, nitrosative, and oxidative stress [58]. Furthermore, studies also showed that the preventive potential of SDG and its metabolites could be affected by the breast cancer resistance protein (BCRP/ABCG2) [59].

3.6. Anti atherosclerotic activity

SDG Lignans are platelet-activating factor–receptor antagonists that would inhibit the construction of oxygen radicals by polymorphonuclear leukocytes, SDG as an antioxidant, reduces hypercholesterolemic atherosclerosis [60]. Long-term usage of SDG suppresses and declines the development of hypercholesterolemia and declines the development atherosclerosis [61].

3.7. Antibacterial activity

SDG exerts an exceptional antibacterial activity against seven different Gram positive and Gram negative bacteria. [62] The SDG extracts were active against the six bacterial species *Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Agrobacterium tumefaciens, Bacillus cereus*, and *Escherichia coli* [63].

3.8. Reno protective activity

SDG showed the reno protective effects in rats through correction of hyperglycemia attenuation of oxidative/nitrosative stress markers; down regulation of renal expressions of inflammatory markers NF-κB, TNF-α, and iNOS; along with upregulation of renal expressions of antiapoptotic markers survivin and Bcl-2 [64].

3.9. Effects on Mental Stress:

SDG inhibited stress-induced behavioral changes, while treatment with high doses of SDG reversed chronic stress-induced increase in serum corticosterone and adrenocorticotropic hormone levels [65].

3.10. Safety aspects

Animal and human studies furnished evidences that flaxseed and its lignan extracts prove to be safe. A recent study reported that SDG administration for 4 weeks had no adverse health effects in female rats. [66] In addition SDG does not appear to negatively affect bone strength in young male and female rats [67]. Studies in older adults about 60-80 years for six months proved that SDG supplementation (300mg/day) in a frail, complex population causes no significant adverse outcomes [68]. Human studies have found that lignan capsules are well tolerated [69]. Furthermore evidences shows that the participants did not report any adverse events in a study that used SDG supplementation at 300 and 600 mg/d [51]. Therefore, 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, while animal studies suggest that pregnant women should limit their exposure [70]. Additional to these, there are no prominent side effects or toxicity of the lignan usage although there are considered to have fewer side effects due to their natural origin. However, sufficient data is still missing about dosages and long-term studies.

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