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Therapeutic Potential of Secoisolariciresinol Diglucoside: A Plant Lignan

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ABSTRACT
Secoisolariciresinol diglucoside (SDG) is a plant lignan mainly found in dietary food and various plants. It belongs to a bioactive polyphenolic chemical class. SDG and its metabolites (mammalian enterolignan) are having various pharmacological activities, viz., antioxidant, partial agonist to estrogen receptor and inhibitor of tyrosine kinase and topoisomerase. Although, human studies are limited, its pharmacological actions explain its use in diabetes, atherosclerosis, breast cancer, colon cancer, prostate cancer and in cardiovascular disease.

Keywords: Secoisolariciresinol diglucoside, plant lignan, polyphenols, antioxidant, tyrosine kinase inhibitor, topoisomerase inhibitor.

INTRODUCTION

Plant lignans are biophenolic compounds and was first identified in 19th Century from woody tissues of trees. Several hundreds of lignans have been documented since then in roots, stem, cereals, oilseeds, nuts, legumes and fruits. [1] Nowadays, with the growing interest towards nutraceuticals, plant lignans are becoming important therapeutically active class of compounds because of their putative beneficial health effect such as antitumor, antioxidant, both estrogenic and antiestrogenic activity [2] and protection against coronary heart disease. [3] This plant lignans can be converted by intestinal bacteria into the mammalian lignan such as enterolignans, enterodiol and enterolactone. [4-6]

Secoisolariciresinol diglucoside (SDG) and matairesinol are the major lignans with traces of pinoresinol, lariciresinol and isolariciresinol found in roots, stem, cereals, oilseeds, nuts, legumes and fruits. [1-2] Flax seed (*Linum usitatissimum* L.) is the richest dietary source of lignans, with SDG as a major compound (% yield being 0.37%), besides that sesame seed, pumpkin seeds, cereals (triticle and wheat), leguminous plant (lentils, soyabeans), fruits (pears, prunes) and certain vegetables (garlic, asparagus, carrot) also contain traces of lignans, but concentration in flaxseed is about 1000 times as high as found in other food sources. [7]

PHARMACOKINETICS OF PLANT LIGNANS

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Table I: Lignans in selected food [8-9]

Food and foods group		Secoisolariciresinol diglucoside content (µg/g)
Seeds	Flaxseed	3699
	Sunflower	6.1
	Caraway	2.21
	Pumpkin	213.7
	Soybean	2.73
Legumes	Peanut	3.33
	Pigeon pea	0.5
	Urad Dahl bean	2.4
Nuts	Walnut	1.63
	Almond	1.07
	Blackberry	37.1
	Lingberry	15.1
Berries	Strawberry	12.1
	Cranberry	15.1
	Red currant	1.6
	Oatmeal	0.1
Cereals	Oat bran	0.24
	Rye meal, whole grain	0.5
	Rye bran	1.32
Vegetables	Broccoli	4.14
	Garlic	3.79
	Carrots	1.92
Coffee and Tea	Arabica coffee (instant)	7.16
	Green tea	24.6
	Black tea	15.9

Bioavailability can be defined as the fraction of the ingested plant lignans that is absorbed and can be used for metabolic process (internal exposure) and storage in the body. Following metabolism of plant lignans in the human colon, the metabolites, enterodiol and enterolactone reach the circulation and target tissues. As metabolism is extensive, enterodiol and enterolactone might be more important for potential health effect. The bioavailability of lignans can be

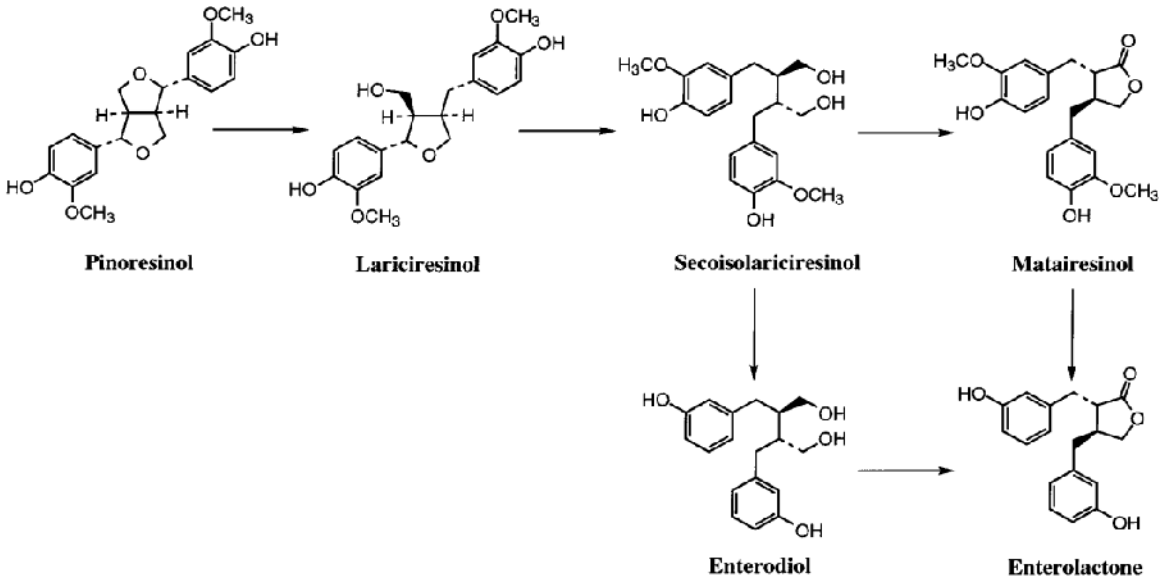

Fig. I: The possible metabolic pathway for transformation of plant lignans to enterolignans by colonic microflora.

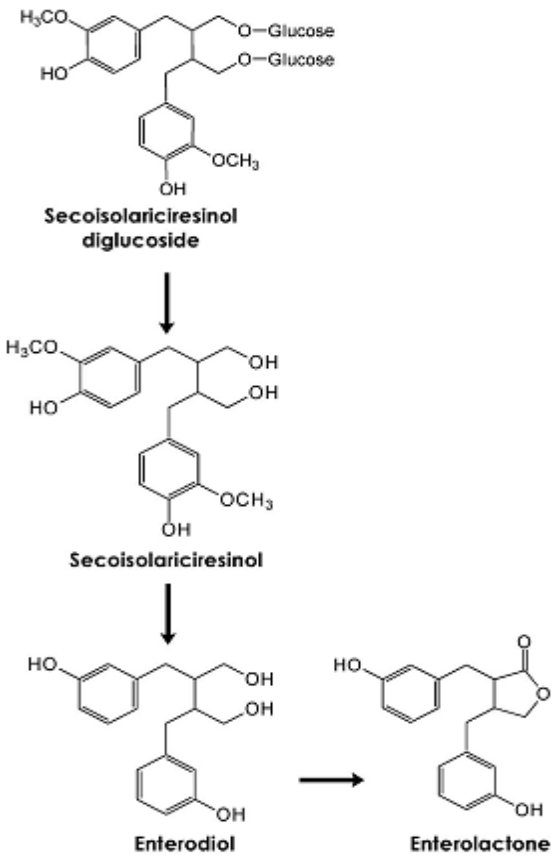

Fig. II: Conversion of SDG by bacteria in colon.

determined by several process: (a) Conversion of plant lignans to enterolignans in the human colon; (b) Absorption of enterolignans from the colon, which determines whether or not enterolignans become available in blood circulation; (c) Distribution and metabolism, which determines whether metabolites reach the target tissues where they can be have an effect or further metabolized. Finally, (d) Enterolignans are excreted from the body via faeces or urine (Fig. III).

Various factors may influence lignan bioavailability such as intestinal microflora, antibiotic use, food matrix, type and form (aglycone or conjugated) of plant lignan, chronic exposure, and other host related factor like age and gender. [10]

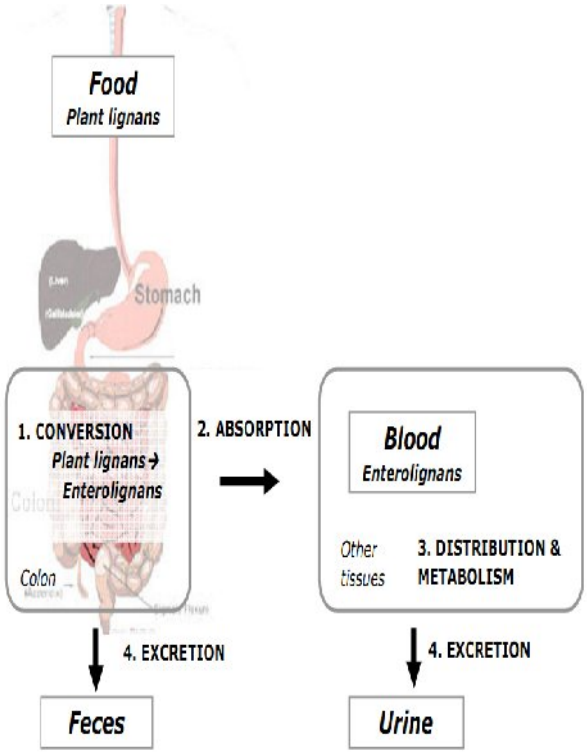

Fig. III: Schematic overview of main bioavailability of lignans.

After consumption of SDG, a small fraction is absorbed as such in the small intestine [11], and excreted in urine. [12-13] However, the largest fraction of the SDG is transported to colon and metabolized by intestinal flora (Fig. II). The importance of microflora in the metabolism of SDG was studied in germfree rats. [14-15] Although the intestinal bacteria play a crucial role in lignan metabolism, few studies had been published that identify organism involved in lignan breakdown. Two anaerobes (*Peptostreptococcus* and *Eubacterium*) catalyze the demethylation and dehydroxylation of SDG. [16] Recently, two microorganisms

Peptostreptococcus productus and *Eggerthella inta* were isolated that were able to demethylate and dehydroxylate SDG and pinoresinol. However, concentrations of enterolactone are usually higher than enterodiol in humans. [17] One bacterial strain (ED-Mt61/PYCt-s6) was identified to be responsible for transformation of enterodiol to enterolactone. [18]

SDG and majority of lignan converted to enterolignans are absorbed by the large intestine into the blood stream or directly excreted via faeces. Plasma enterodiol and enterolactone circulate either as glucouronide and sulfate conjugates or as free forms. [19] They are excreted via urine or bile, in urine; enterodiol and enterolactone are excreted in conjugated forms; primarily as monoglucouronides (85 and 95% respectively) with small percentage being excreted as monosulfates (2-10%) and free aglycones (0.3-1%). [20-21] Conjugated enterolignans that are excreted via bile can undergo enterohepatic circulation (i.e. excreted through bile duct into the intestinal tract, further metabolized in the colon, and reabsorbed from the large intestine into the bloodstream). [15, 22] The mean residence time and half lives measured after single dose of SDG (0.9 mg SDG/kg bodyweight) in healthy men and women indicates that enterolignan accumulate in plasma when consumed 2-3 times a day and reach steady state. [23]

PHARMACOLOGICAL ACTIVITIES OF SECOISOLARICIRESINOL DIGLUCOSIDE (SDG)

Antioxidant activity: The plant lignans demonstrated extreme radical scavenging activity. In both lipid and aqueous, *in-vitro* model systems SDG and its metabolites appeared as antioxidant. All three lignans significantly inhibited the linoleic acid peroxidation at 10 and 100µM over a 24-48 h of incubation at 40°C. [24-25] However, it has been demonstrated that enterodiol and enterolactone were not effective in preventing H_2O_2 induced DNA damage in HT-29 cells and enterolactone did not reduced intracellular oxidative stress at similar concentration. [26]

Antiatherosclerotic effect: One of the most etiological reasons of atherosclerosis is the release of inflammatory mediators such as interleukin (IL-1), tumor necrosis factor (TNF), leucotriene B_4 (LTB_4). These all mediators are known to stimulate polymorphonuclear leukocytes (PMNLs) and monocytes to produce oxidative free radicals (OFRs). As the flaxseed is the richest source of the SDG, [6] supplementation of flaxseed was reduce the level of OFRs and hence, prevent the development of hypercholesterolemic atherosclerosis and aortic atherosclerosis by 46% markedly without lowering serum cholesterol. [27-30]

Anticancer activity: Secoisolariciresinol diglucoside and other lignans are phytoestrogen, because of their potential estrogenic and antioxidant activity had been studied for various cancer protective mechanisms. Supplementation of richest lignan source flaxseed reduced the epithelial cell proliferation by 38.8 - 55.4% and nuclear aberration by 58.8 - 65.9% in female rat. [31-32]. Enterolignans can bind to estrogen receptor α and β [33] and block or antagonize the effect of estrogen in some tissues. [34] Extensive work had been done to study the chemoprotective action of SDG and enterolignans on mammary cells. Supplementation of SDG reduced the risk of breast cancer, and showed antiproliferative effect on the breast, positive effect on lipoprotein profile and bone density in post menopausal women. [24, 35-38] It showed the suppression of mammary tumorigenesis by its partial estrogenic activity, antioxidant activity or reduction of plasma insulin like growth factor-1. [38-41] Besides, its antioxidant and partial estrogenic activity of SDG and enterolignans also affect to beta glucouronidase activity, which may be the cause of protective effect against colon cancer. It has been observed that pretreatment of flaxseed decrease the risk of colon carcinogenesis, with reduced total number of aberrant crypts and foci significantly by 41-53% and 48-57% respectively. [38, 42-43] Metabolites of SDG also appeared to influence steroid metabolism *in- vitro*, not only by acting on steroid receptor but also by steroid metabolism, for e.g. sex hormone binding globulin synthesis [44-45] 5α-reductase and 17-β hydroxyl-steroid dehydrogenase. [46] On the virtue of these all property and inhibition of tyrosine kinase and topoisomerase contribute the lower incidence of prostate cancer. [47]

Anti-diabetic activity: It has been demonstrated that SDG prevented development of diabetes mellitus by 75%. The reactive oxygen species play an important role in development of debates mellitus (DM) therefore it was suggested that the antioxidant activity may be playing role for its antidiabetic activity. [48-49]

Effect on Cardiovascular system: There are several mechanisms by which SDG protect against cardiovascular diseases. It appeared beneficial role in endotoxic shock. [25, 50] Apart from reducing cholesterol level it also induced angiogenesis mediated cardioprotection by increased neovascularization in the peri-infarct zone, leading to less ventricular remodeling. Thus, SDG is a great clinical potential for treatment of ischemic heart disease. [51]

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