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Flaxseed as a functional food source†

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Abstract: Flaxseed is emerging as one of the key sources of phytochemicals in the functional food arena. In addition to being one of the richest sources of α-linolenic acid oil and lignans, flaxseed is an essential source of high-quality protein and soluble fibre and has considerable potential as a source of phenolic compounds. The implications of diets containing flaxseed or its components for human nutrition and disease prevention are analysed in this paper. Results of the first meta-analysis examining the relationship between intake of flaxseed or its components and risk reduction of disease in humans is presented. Some areas of potential opportunities and impact of using flaxseed or its components in the diet are highlighted.

Keywords: flax; *Linum usitatissimum*; functional food; α-linolenic acid; lignans; meta-analysis; patents; disease prevention; flaxseed; flaxseed components

INTRODUCTION

Flax (*Linum usitatissimum*) is an economically important oilseed crop, especially for Canada, which produces about 40% of the world's flaxseed and is the world's largest exporter of flaxseed, representing about 75% of the global flax trade.[1] The European Union, the world's largest crusher of flaxseed (about a third of world flaxseed crush), imports about two-thirds of the world flaxseed trade. The world demand for flaxseed is currently dominated by the industrial uses of flaxseed oil. However, flaxseed is making great strides in the world's food supply, and demand for human food and livestock markets is expected to increase owing to the unique properties of this ancient crop.

Flaxseed consumption in various forms as a food ingredient and for its medicinal properties dates from 5000 BC since its cultivation.[2] It is therefore not surprising that flaxseed is the most prominent oilseed studied to date as a functional food, since it is a leading source of the omega-3 fatty acid α-linolenic acid (ALA) (52% of total fatty acids) and of phenolic compounds known as lignans ($>500\,\mu g\,g^{-1}$, as is basis).[3] These and other components of flaxseed incorporation in the diet are particularly attractive for the development of foods with specific health advantages.

META-ANALYSIS

The demonstration of clinical activity associated with the consumption of flaxseed led the US National Cancer Institute (NCI) to target flax as one of the six plant materials for study as cancer-preventative foods.[4] Although the physiological effects of flaxseed and its components are well known, evidence supporting and/or capitalising on the viable market growth for functional foods has not been properly documented. In this context a computerised literature search on Medline was performed to identify trials assessing clinical end-points of intake of flaxseed or its components in reducing the risk of diseases. This systematic review of the effectiveness of flaxseed and its components on humans identified 24 clinical studies. Nineteen of these trials were actual clinical studies, 11 of which involved flaxseed oil (Table 1). However, only 12 studies, six each with flaxseed and flaxseed oil, involving a total of 208 people, met all the criteria of well-designed clinical trials.

Collectively, the results generated by three studies[5–7] on lipid metabolism suggest that flaxseed oil does not alter serum chemistry, but, in large doses, triacylglycerol levels are reduced. The clinical relevance of the hypothesis that ALA of flaxseed oil protects against cardiovascular disease is considerable and is supported by four studies.[8–11] Thus a simple addition of flaxseed oil to canola oil in a 1:3 ratio can beneficially mediate the effects of ALA on the eicosanoids, producing significant reduction in the risk of cardiovascular disease.[11] Flaxseed oil is a potent inhibitor of pro-inflammatory mediators[12,13] even when used in domestic food preparation. This advantage of flaxseed oil can be positively utilised in the development of novel anti-inflammatory therapies

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with or without pharmaceutical products for target populations.[14,15]

Three studies[16–18] concluded that consumption of flaxseed either raw or defatted reduces total and LDL cholesterol in humans, confirming the multicomponent cardioprotective effect of flaxseed. In addition to the hypocholesterolaemic effect, flaxseed confers beneficial renal function in patients suffering from lupus nephritis,[18] is well tolerated and does not compromise antioxidant status.[19] Studies in women[20–24] show the vital role of flaxseed in mediating bone health and its strong phytoestrogenic and therapeutic effect in reducing the risk of hormone-related cancers. This systematic review supports other epidemiological studies indicating that consumption of flaxseed may be protective against coronary heart disease, immunorenal injury and hormonal cancers.

FLAXSEED PATENTS

Since health claims are not proprietary and the investment community is more comfortable with the nutraceutical and functional food business model when it offers patent protection, patents on flaxseed were searched. Thirty-four matching documents with 'flaxseed' in the title or abstract were retrieved from the European patent office. However, only 18 of these documents dealt with flaxseed when multiple filing and patents without title were taken into consideration. These patents (Table 2) can be classified based

Table 1. Review of clinical studies with flaxseed and its components

Component/effect	*Study*	*Ref*
Flaxseed oil		
Lipid metabolism	Flaxseed oil fed to 10 healthy men for 126 days did not alter serum triglyceride, HDL and LDL cholesterol and serum ALA concentrations	5
	Flaxseed oil (35 mg kg^{-1} body wt) fed to 26 normal humans for 3 months did not alter plasma triacylglycerol levels	6
	Only large amounts of flaxseed oil supplementation reduced triacylglycerol levels	7
Eicosanoid mediation	Increasing dietary ALA elevates tissue eicosapentaenoic acid (EPA) concentrations in a predictable manner in healthy volunteers	8
	Diets high in flaxseed oil and low in linoleic acid fed to 30 healthy male volunteers for 4 weeks elevated plasma EPA concentration by 2.5-fold similar to those associated with fish oil supplementation	9
	Platelet EPA more than double with intake of 40 g flaxseed oil in five individuals for 23 days. ALA offers protective effect against cardiovascular disease	10
	A 7 week pilot study of n-6/n-3 ratio of polyunsaturated fatty acid (PUFA) 28:1 to 1:1 using canola and flaxseed oil (3:1) showed that dietary ALA is an effective modulator of thromboxane and prostacyclin biosynthesis. Eicosanoid-mediated effects of ALA were similar to those elicited by marine lipids	11
Anti-inflammatory	Use of flaxseed oil in domestic food preparation for 4 weeks inhibits interleukin production (30%) and tumour necrosis factor (74%) in healthy volunteers	12
	Use of flaxseed oil in domestic food preparation inhibits production of cytokines	13
	Supplementation of ALA for 3 months to 22 patients with rheumatoid arthritis showed no beneficial effects	14
	Arterial functions improved for 15 obese people on a high-ALA/low-fat diet (20 g from margarine products based on flaxseed oil)	15
Flaxseed		
Lipid metabolism	Flaxseed consumption (50 g ground raw flaxseed day^{-1}) for 4 weeks increased plasma ALA and urinary thiocyanate excretion in healthy female volunteers. Flaxseed lowered serum and LDL cholesterol and postprandial glucose response	16
	Partially defatted flaxseed (50 g day^{-1}) reduced total cholesterol in 29 people after 3 weeks consumption in a controlled cross-over trial	17
Anti-inflammatory	30 g flaxseed day^{-1} reduced total and LDL cholesterol and conferred benefit in terms of renal function, inflammatory and artherogenic mechanisms in eight patients suffering from lupus nephritis	18
Nutrition	Flaxseed intake (50 g day^{-1}) for 4 weeks has modest beneficial effects on nutritional status without compromising antioxidant status	19
Skeletal health	Flaxseed (38 g $days^{-1}$ as muffin and bread) consumed as part of the diet for two 6 week periods exerted beneficial effect (reduced rate of bone resorption) in 38 postmenopausal women	20
Lignan biomarker	Ground flaxseed diets (10 g day^{-1}) increased faecal excretion of lignans (marker of anticarcinogenic activity) in 13 women	21
	Flaxseed powder (10 g day^{-1}) supplemented to the diet increased lignan excretion in 18 women	22
	Ground flaxseed (0, 5, 10 g day^{-1}) consumed in addition to usual diets increased urinary oestrogen metabolite excretion in a linear dose–response fashion in 28 postmenopausal women	23
	Nine healthy young women supplementing their diets with 5, 15 or 25 g raw or 25 g processed flaxseed for 7 days showed dose-dependent urinary lignan response to raw flaxseed	24

on the components of flaxseed and/or target areas into flaxseed oil (three patents), lignans (four patents), flaxseed gums (seven patents) and animal feed (four patents). According to these patents, flaxseed oil as a source of ALA prevents hypercholesterolaemia[25] and thrombosis[26] and reduces platelet adhesiveness.[27] Flaxseed lignans extracted from defatted meal[28] control renal diseases such as lupus nephritis[29] and combat menopause symptoms[30] and early stages of cancer[31] when combined with soybean isoflavones. Extraction of flaxseed gums dates back to 1932 and has constantly been revisited.[2] Hence it is not surprising to encounter numerous patents[32–35] on the extraction of flaxseed gum, especially since the soluble fibre has been implicated in the management of hyperglycaemia and hypercholesterolaemia in humans.[36] The presence of high lignan content in the gum[33] creates synergistic effects potent enough to inhibit colon cancer in rats.[37] The physicochemical and functional properties of flaxseed gum[38] provide beneficial effects as a saliva substitute,[39] a mucoadherent[40] and a drug-releasing agent useful for the nutraceutical market. Flaxseed meal shows physiologically favourable effects as a feed by enhancing ALA and phytoestrogenic status[41–44] in animals.

POTENTIAL FUNCTIONAL FOOD COMPONENTS FROM FLAXSEED

When the results from the meta-analysis and patent search are compared, the lack of clinical studies on flaxseed gum and protein becomes clearly evident. One reason for this dearth of clinical studies on flaxseed gum and protein may be the increased understanding of, and belief in, secondary plant substances as the only bioactive phytochemicals. Both protein and gums are abundant major components of flaxseed and as such would be the most economical targets for functional foods. Flaxseed gum has nutritional value as a dietary fibre; as such it appears to play a role in reducing diabetes and coronary heart disease risk, preventing colon and rectal cancer and reducing the incidence of obesity.[36] Flaxseed gum behaves like typical viscous fibres with the ability to reduce blood glucose response[45] and flatten blood glucose profile. Reducing blood glucose response contributes to improving overall blood glucose control and is likely to be beneficial for individuals with glucose intolerance.

Flaxseed protein may also influence blood glucose because of its interaction with the gums and also by stimulating insulin secretion, resulting in reduced glycaemic response.[46] The interaction between flaxseed protein and soluble polysaccharides may play a significant role in reducing colon luminal ammonia, thereby protecting against the known tumour-promoting effects of ammonia.[47] Lignans are also known to have strong protein-binding properties,[48] which may suggest some partial chemopreventive effect of flaxseed in conjunction with lignans. Proteins with high levels of branched-chain amino acids (BCAA: valine, leucine, isoleucine), low content of aromatic amino acids (AAA) and high Fischer ratio (BCAA/AAA) are being sought for producing physiologically functional foods for specific needs, such as in patients with malnutrition associated with cancers, burns, trauma

Table 2. Review of patent search 'flaxseed' on esp@cenet database

Component	*Claims*	*Ref*
Flaxseed oil	ALA (1–10%) of total fatty acid content of oil reduces blood cholesterol levels	25
	High-ALA-content oil with vitamin E prevents thrombosis, decreases atherosclerosis and reduces blood cholesterol	26
	Flaxseed oil containing flax phospholipids (3% by wt) reduces platelet adhesiveness in humans	27
Lignans	Lignans are extracted from defatted flaxseed meal—20 mg g^{-1} defatted meal	28
	SDG from flaxseed administered in pure form controls lupus nephritis in humans	29
	Flaxseed lignans combined with isoflavones (soy flour) and inulin as a drink mix powder are intended to act on menopause symptoms in women	30
	Cookies/biscuits made from flax lignans combined with genistein (soy) combat cancer	31
Flaxseed gum	Flax gum is obtained at 82–92% extraction rate by a process that includes grinding, airflow separation and sieving (50–100 mesh)	32
	Flax gum obtained by dry dehulling is claimed to have high lignan content	33
	Flaxseed mucilage yields D-galacturonic acid on acid hydrolysis	34
	Process is designed to obtain flax protein and flax mucilage for use in baking	35
	A dietary fibre composition consisting of subfractions of wheat bran, soy and flaxseed inhibits colon cancer in rats	37
	Flaxseed polysaccharides act as a saliva substitute (against xerostomia) and as a carrier of pharmaceuticals (oral use)	39
	Flaxseed mucilage functions as a mucoadherent in the gastrointestinal tract, a cryoprotective and a drug-releasing agent	40
Flaxseed	Feed additive containing flaxseed meal has physiologically favorable effect	41
	Flaxseed meal mixed with feed and vitamins (100–110 g day^{-1}) and fed to poultry enriches eggs with ALA	42
	Flaxseed meal enhances n-3 fatty acids of microbial biomass for aquaculture	43
	Feeding ground flaxseed with zinc increases live birth to female animals	44

Table 3. Amino acid characteristics of flaxseed proteins

	BCAA (Val+Leu+Ile)	*AAA (Phe+Tyr)*	*Fischer ratio*	*Lys/Arg*	*Arg+Glu+His*	*Met+Cys*
High-molecular-weight 12S protein[a]	16.0	8.2	2.0	0.25	34.8	4.5
Low-molecular-weight protein[b]	16.0	3.8	4.2	0.37	49.7	8.7
Globulins[c]	13.0	7.5	1.7	0.43	35.9	NR
Albumins[d]	13.0	8.1	1.6	0.50	42.2	NR
Low-molecular-weight 2S protein	12.4	3.6	3.4	1.00	31.0	8.7
Flow-through (DEAE fraction)	11.7	4.3	2.8	0.39	50.4	4.4
0.20 M NaCl fraction	14.8	8.1	1.8	0.23	19.1	1.9
Soy	17.0	8.0	2.1	0.88	32.1	3.0

NR, not reported.
[a] Data calculated from Ref 51.
[b] Data calculated from Ref 52.
[c] Data calculated from Ref 53.
[d] Data calculated from Ref 54.

and liver failure, and for nutritional support of children with chronic or acute diarrhoea or milk protein allergies.[49] Flaxseed protein and its individual fractions are high in BCAA and Fischer ratio, comparable to that of soybean (Table 3). Some flaxseed protein fractions with BCAA and Fischer ratio as high as 25 g per 100 g protein and 4.7 respectively provide the desirable levels required in diet formulations for patients with liver disease. The lysine/arginine ratio, a determinant of the cholesterolaemic and atherogenic effects of a protein,[50] is low for flaxseed protein, suggesting that it is less lipidemic and atherogenic than soybean protein with a lysine/arginine ratio of 0.88. Flaxseed protein is also an excellent source of arginine, glutamine and histidine, the three amino acids known to have strong effects on the immune functions of the body. The high cysteine and methionine content of flaxseed proteins can boost the body's antioxidant levels, potentially stabilising DNA during cell division and reducing the risk of certain forms of colon cancer.

CONCLUSIONS

The most researched biological activities of flaxseed have been relegated to ALA, lignans and, to a lesser extent, soluble polysaccharides (gum), since flaxseed is the most abundant prominent source of these components. However, most of the human studies to date that show beneficial effects have used whole flaxseed, flaxseed flour or defatted flaxseed meal, ie products of commerce. Hence strategies for the economic extraction, modification and clinical evaluation of phytochemicals from flaxseed have to be developed for flaxseed to be a truly functional food. In this regard, lipid composition is continually being modified to meet the demand of target markets; for example, the low-linolenic-acid flax Linola® has already been commercialised. Linola® seed contains oil high in linoleic acid and is therefore potentially an excellent feed to produce conjugated linoleic acid (CLA). Epidemiological evidence suggests that CLA reduces the risk of breast cancer in women, has a cardioprotective effect,[55] reduces body fat, maintains weight loss[56] and controls adult-onset diabetes.[57] Similarly, functional foods obtained by feeding flaxseed to animals, such as omega-3-enriched eggs, are common grocery items in North America.

Although the specific components responsible for the physiological effects are slowly being unravelled, the combined and/or synergistic effects of component interactions have yet to be elucidated. A case in point is the reduced risk of cancer that has been attributed to the biological effects of both ALA and the lignan secoisolariciresinol diglycoside (SDG), and protection against cardiovascular disease attributable to ALA, flaxseed gum and proteins. In the current rush for determining the phytochemical with the most biological activity, some components of flaxseed have received very little attention, and safety issues pertaining to known flaxseed phytochemicals are largely unanswered. Accurate documentation of the therapeutic effects of flaxseed and its components that contribute uniquely to disease prevention, health protection and as a deterrent to degenerative diseases will increase its potential for use as a functional food and food ingredient.

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