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The Pharmacological Evaluation of Flax Seed Oil

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ABSTRACT

Flax seed oil is important food and nutrition sources. It has a low content of saturated fatty acids (9% of all the fatty acids), a moderate content of single saturated fatty acids (about 18%) and a high content of unsaturated fatty acids (about 73%). This oil can be used as a nutritional supplement and is significant in respect of containing omega-3 fatty acid, especially a high level of ALA and a low level of omega-6 fatty acids. The protein content of flax seed varies between 20-30%, and it contains a high level of globulin (linin and conlinin) and gluten. The proportion of non-protein nitrogen constitutes 21.7% of the total nitrogen content. The total nitrogen content has been reported as 3.25g/100 grams of seed. Today, flax seed stands out among the functional additives in the food industry due to the presence of α-linolenic acid, lignans and fibers in its content. Among the oils obtained from seeds, flax seed comes into prominence since it has high contents of α-linoleic acid (ALA, 18:3n-3) and lignans. Flax seed contains oil by 35-45%, and 45-52% of it consists of ALA. ALA is classified as omega-3 group fatty acid and has anti-inflammatory, antithrombotic and antiarrhythmic characteristics.

Key Words: ALA, Flax seed, Oils, Pharmacological effects

Abbreviations:
LDL : Low density lipoprotein
HDL : High density lipoprotein
VLDL : Very low density lipoprotein
ALA : α-linolenic acid
TNF : Tumor necrosis factor
IL : Interlocim
EPA : Eicosapentaenoic Acid
DHA : Docasahexaenoic Acid
Mac-3 : Makrophages Marker-3
SECO 2: Secoizolarisiresinol-2
SDG1: Secoizolarisiresinol diglikozid-1

1 INTRODUCTION:

Flax (Linum usitatissimum in Latin) is the most common species of the genus Linum in the family Linaceae. It is a plant that blooms with silk-like, bluish or yellow flowers between June and August. This species is a herbaceous annual cultivated plant that can have a length of 30-90 cm. It has narrow, lineal, three-veined, hairless, pointed and non-bilateral leaves, and pale blue flowers extending towards the upper sections of the stem. There are mucilage agents in the epidermis of the seed at a rate of 3-10%. Proteins are available at a rate of about 25% (B.Lei et al., 2013) [1] . Fixed oil is available at a rate of 30-45% (Zeybek U., Haksel M., 2011) [2] .

Almost every part of the flax plant has a commercial use, and especially flax seed has great significance for the food and nutrition sectors. Strong and durable fibers in its structure are particularly of great importance in terms of areas of use. Flax seed contains oil rich in omega-3, digestible proteins and lignans. Today, flax seed stands out among the functional additives in the food industry due to ALA (α-linolenic acid), lignans and fibers in its structure.

Flax seed has a flat and oval shape (2.5x5.0x1.5mm) and a different appearance from dark colors to the yellow color (Freeman, 1995) [3] . In its structure, there is a shell, a thin endosperm, two embryos and embryo nucleus. 55% of flax seed consists of embryo, 36% of shell and endosperm and

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4% of embryo nucleus (Bhatty, 1995) [4] .

Chemical Composition of Flax Seed Oil

Among the oils obtained from seeds, flax seed oil comes into prominence due to its high content of α-linolenic acid (ALA, 18: 3n-3) and lignans. Flax seed contains oil by 35-45% and 45-52% of it consists of ALA (Bhatty, 1995) [5] . ALA is classified as omega-3 group fatty acid and has anti-inflammatory, antithrombotic and antiarrhythmic characteristics (Simopoulos, 1999) [6] . Fish oil is included in diets as a source of omega-3, and likewise, it is possible to use flax seed oil as a source of vegetarian omega-3. Flax seed constitutes a concentrated source of lignan, which is anticarcinogenic and especially effective against breast and colon cancers (Axelson, 1982 Madhusudhan, 2000) [7] .

General information about the content of flax seed is stated in Table 1. Flaxseed contains oil by 35-45% oil. Embryos in the seed constitute the part with the highest oil content, by 75% (Bhatty, 1995) [8] . The oil content of the embryo nucleus is stated as 44.9%. Testa and endosperm, on the other hand, contains oil by 22.9% (Dorrell, 1970) [9] .

Nutrients	Whole Flaxseed (%)					Meal (%)	Full-fat flour (%)
Moisture	6.5	7.1-8.3	7	6	—	—	4.50
Lipids	37.1	31.9-37.8	41	30-45	40-45	10-12	37
Protein	20.3	26.9-31.6	20	20-25	24-26	43-47	22.4
Carbohydrates	28.9	—	—	30-35	25-27	34-38	—
Total Dietary Fiber	4.8	36.7 - 46.8	28	10	—	—	8.2
Insoluble Fiber	—	30	—	—	—	—	
Soluble Fiber	—	10	—	—	—	—	
Minerals	2.4	—	4.0	4.0	~4.0	~7.0	—
Energy	530	—	—	—			—
Calcium, mg	170	—	—	—			—
Phosphorus, mg	370	—	—	—			—
Iron, mg	2.7	—	—	—			—
Carotene μg	30	—	—	—			—
Thiamin, mg	0.23	—	—	—			—
Riboflavin, mg	0.07	—	—	—			—
Niacin, mg	1.0	—	—	—			—

*Source: Gopalan et al., 2007; (Hettiarchchy, 1990); Flax Council of Canada; (Bhatty and Cherdkiatgumchai, 1990; Budavari,1996; Daun et al., 2003); Mazza, 2008; Hussain et al., (2006).

Table 1. Composition of flax seed (Singh, 2011)

Seeds contain coarse substances by 25% (3-6% mucilage, 4-7% nutritional fibers) oil by 30-45%, protein by 20-27%, mineral, vitamin, lignan precursors, linustatin, neolinustatin, linamarine and enzyme by 3-5%. The water content of the seeds changes between 5-14% (EMA, 2006) [10] .

Flax seed oil is available in two separate parts with a diameter of 1.3 μm. The majority of these oil components are comprised of neutral oils and their ratio has been determined as 98% (Tzen, 1993) [11] . Flax seed contains palmitic acid by 5-6% (16:0), stearic acid by 3-6% (18: 0), oleic acid by 19-29% (18:1n-9), linoleic acid by 14-18% (18:2n-6) and ALA by 45-52% (18:3n-3) (Bhatty, 1995) [12] . Even though flax s eed h as h igh c ontents o f a ntioxidant n utrients (e.g. Beta carotene), the traditional flax seed oil is oxidized after being extracted and purified (Singh, 2011) [13] . General information about the content of flax seed oil is stated in Table 2.

Flax seed oil has a low content of saturated fatty acids (9% of all the fatty acids), a moderate content of single saturated fatty acids (18%) and a high content of unsaturated fatty acids (73%) (Cunnane, 1995) [14] . Flax seed oil obtained via the cold press technique without solvent extraction is suitable for human use, however, it is not recommended for cooking. This oil can be used as a nutritional supplement and is significant in respect of containing

Fatty acids	Whole linseed (%)		Linseed oil (%)		
Palmitic acid C 16:0	4.6–6.3	—	4.21–8.71	6.0	5.0
Stearic acid C 18:0	3.3–6.1	—	3.52–8.17	2.5	3.6
Oleic acid C18:1	19.3–29.4	3.6 g	22.17–41.72	19.0	19.5
Linoleic acid C18:2	14.0	3.2 g	4.82–19.13	24.1	15.6
Linolenic acid C 18:3		11.4g	33.22–54.79	47.4	55.8

Table 2. Fattyacid composition of flax seed oil (Singh,2011)

omega-3 fatty acid, especially a high level of ALA and a low level of omega-6 fatty acids. The protein content of flax seed varies between 20-30%, and it contains a high level of globulin (linin and conlinin) and gluten, but no albumin (Care, 1954) [15] . The proportion of non-protein nitrogen constitutes 21.7% of the total nitrogen content. Flax seed proteoses have high contents of arginine and glutamic acid. The total nitrogen content has been reported as 3.25g/100 grams of seed (Gopalan, 2007) [16] . Lysine is the most restricted amino acid. Amino acid content of flax seed is shown Table 3.

Amino acid	Brown Flax (omega) g/100 g protein	Yellow flax (Norlin) g/100 g protein	Flaxseed mg/g of N
Alanine	4.4	4.5	—
Arginine	9.2	9.4	560
Aspartic Acid	9.3	9.7	—
Cystine	1.1	1.1	120
Glycine	5.8	5.8	—
Histidine	2.2	2.3	120
Isoleucine	4.0	4.0	310
Leucine	5.8	5.9	360
Lysine	4.0	3.9	230
Methionine	1.5	1.4	100
Phenylalanine	4.6	4.7	270
Proline	3.5	3.5	—
Serine	4.5	4.6	—
Threonine	3.6	3.7	210
Tryptophan	1.8	NR	100
Tyrosine	2.3	2.3	180
Valine	4.6	4.7	320

Table 3. Amino acid content of flax seed

In flax seed, there are also water-soluble and water-insoluble fibers together with lignan. The ratio of water-soluble fiber to water-insoluble fiber ranges between 20:80 and 40:60. The water-insoluble fibers contain cellulose and lignin and the water-soluble fibers contain mucilage gums in their composition. 8% of the weight of flax seed is constituted by mucilage. The mucilage gums become viscous when combined with water or other liquids and have great significance with regard to laxative properties. SECO 2 [2, 3-di-(methoxy-4-hydroxybenzyl) butane-1,4-diol] constitute the largest part of the lignans in flax seed in the form of diglycoside SDG1 conjugate. Within nutrients, the richest source of SDG1 is flax seed (7mg/g or 3.7 mg SECO 2/g) (Singh, 2011) [17] .

2 MATERIALS AND METHODS:

This review is based on searches of electronic database, including PubMed, Google Scholar using the combination of

"flax seed", "oils", "pharmacological effects", "as keywords. Articles regarding the agriculture and pharmaogical effects or benefit of flax ssed oil were excluded. Several other studies and reviews were also included to provide essential information.

3 RESULTS AND DISCUSSION:

Effect Mechanism and Pharmacological Effects

Support for the treatment of cardiovascular diseases due to its antiatherosclerotic characteristics (preventing vascular stiffness)

As a result of the recent studies, it has been shown that flax seed oil is an alternative source of omega-3 of vegetable origin. Flax seed is an herbal resource rich in ALA, a derivative of omega-3 fatty acid. In the diets prepared for adults, 2.22 g ALA should be taken within a 2000-calorie diet on a daily basis. Digested flax seed can supply this necessary amount of ALA for the body. The amount of ALA increases two weeks after flax seed begins to be taken (Simopoulos, 2000 Francois, 2003 Gebauer, 2006) [18–20] .

In these studies, it was demonstrated that the prevalence of primary cardiovascular diseases was inversely proportional to the ALA intake, that is, the prevalence of these diseases decreased with the increase in the ALA level.

In a study conducted by Djousse et al., the relationship between the diet profiles and ALA intakes of 4584 participants and coronary diseases was assessed. In this study, the ALA intake values (g/day) were recorded as 0.53, 0.67, 0.78, 0.90 and 1.14 for men, and as 0.46, 0.58, 0.65, 0.76, and 0.96 for women. The prevalence of coronary diseases was found to be 1.0, 0.77, 0.61, 0.58 and 0.60 for men (p=0.012) and 1.0, 0.57, 0.52, 0.30 and 0.42 for women (p=0.014) (Djousse, 2001) [21] .

In another study, there were investigations on 2004 participants between the ages of 32 and 93. Calcified plaque scores in the coronary artery were evaluated via computed tomography. In this study, the daily intake for linolenic acid was specified as 0.82±0.36 g/day for men and 0.69± 0.29 g/day for women. As a result of this study, it was concluded that there was a decline in the calcified plaque scores in the coronary arteries, inversely proportional to the increase in the linolenic acid intake (Djousse, 2005) [22] .

In another double-blind placebo-controlled study, 120 patients under the risk of acute myocardial infarction were followed up and 2.9 g of ALA supplemented to them on a daily basis. In the assessment implemented at the end of the year, it was discovered that the mortality rate decreased substantially in terms of cardiac-induced death and myocardial infarction compared to the placebo group.

Support for the treatment of cardiovascular diseases due to its antihrombotic and anticoagulant (blood thinning) characteristics

As a result of different studies carried out today, it has been revealed that the presence of Omega-3 fatty acids in nutritional diets is effective in the protection of the heart, taking 0.5-2 grams of omega-3 fatty acid per day has an effect on protection against cardiovascular diseases, and taking higher doses does not have any additional effects (Sacks, 1995). [23]

In a study conducted by Allman et al., the effects of two dietary administrations with high contents and low contents in terms of linolenic acid on platelet aggregation were investigated. The subjects were divided into two groups as the groups taking 40 g of flax seed oil (n=5) and sunflower oil (n=6) for 23 days. Preprandial blood samples were taken at the beginning and end of the experiment and analyzed for platelet fatty acids and platelet aggregation. The values of the group fed with flax seed oil were doubled in terms of the platelet eicosapentaenoic acid (EPA) value, however, no change was observed in the values of the group taking sunflower oil ($p<0.05$). It was demonstrated that the platelet EPA: arachidonic acid ratio, which is a marker of the thromboxane production and potential platelet aggregation, increased in the group taking flax seed oil ($p<0.05$). Moreover, in the group taking flax seed oil, it was shown that the aggregation response induced by 0.75 and 2 micrograms of collagen decreased ($p<0.05$). As a result of this study, the consumption of the oil with a high content of alpha linolenic acid might have protective effects in cardiovascular diseases due to its effects reducing the platelet aggregation (Allman, 1995) [24] .

In a study conducted by Hornstra et al., it was revealed that the flax seed oil had antithrombotic effects in experimental animals (Hornstra, 1979) [25] . It was reported that the incidence of thrombosis was normalized in rats to which saturated fat, cholesterol and 80 mg of flax seed oil per day were administered as nutritional supplement. On the other hand, it was discovered that the risk of thrombosis declined in the rats (80 mg oil/day, 47.2% ALA, n6:n3 ratio 0.38) to which flax seed oil and additional saturated fat were administered as basal dietary supplement (Nordoey, 1965) [26] . In the same study, it was revealed that the risk of thrombosis did not change without the addition of saturated fat into the basal diet. Similarly, in another study conducted by Lee et al., it was put forward that the atherosclerotic plaque formation in rabbits could be prevented with the addition of flax seed oil into their diets (5% oil, 51-55% ALA, n6:n3 ratio:0.30) (Lee, 2003) [27] .

As a source of vegetable omega 3 (ALA) in adults who do not consume fish oil, especially in vegetarians

The human body has the ability of synthesizing many oils it needs. However, the synthesizing of two essential fatty acids (linolenic acid and linoleic acid) within the body is not possible, and they need to be obtained from food. These fatty acids are used for the synthesizing of omega-3 and omega-6, and these two components are necessary for the continuation of the normal body functions. Omega-3 fatty acids are comprised of linolenic acid. The most basic omega-3 is called α-linolenic acid (ALA) and transformed into eicosapentaenoic acid (EPA) and docosahexaenoic acid in the body. In this respect, ALA is the only essential omega-3 fatty acid. ALA is available in many plants such as beans, walnut and fruits. One of the plants with the highest content of ALA is flax seed. Even though fish is indicated as a

source of essential oil, other oils and cholesterol in it and its lack of fibers push this nutrient into the background. Furthermore, mercury and other similar environmental wastes that can exist in high amounts in the fish support this situation. It is believed that vegetable omega-3 is better for human health. In studies, it was shown that vegetable omega-3 had a more stable form. In a study carried out by the European Prospective Investigation into Cancer and Nutrition (EPIC), women who had vegetarian diets had omega-3 with a longer chain in their blood compared to those nourished with fish and meat derivatives. It was reported that a tea spoon of flax seed oil or a table spoon of flax seeds per day would be enough to meet the daily need for ALA (Odeleye, 1991 Williams, 2006) [28, 29] .

Regulating blood lipid values

In studies, declines were indicated in very low density lipoprotein (VLDL) levels of hyperlipidemic people with omega-3 fatty acids (Richter, 1992) [30] .

In other studies conducted on this topic, the moderate effects of flax seed on total blood cholesterol, LDL and HDL were set forth.

In the study conducted by Patade et al., the consumption of 30 g/day of flax seed decreased the total cholesterol level by 7% and the LDL level by 10% in women in the postmenopausal period (Patade, 2008) [31] .

Zhang et al. revealed that the administration of 600 mg/day of SDG (secoisolariciresinol diglucoside) (lignan derivative obtained from flax seed) in hypercholesterolemic patients with an 8-week diet led to a decline in total cholesterol levels by 22% and in LDL cholesterol levels by 27% (Bloedon, 2004) [32] .

In a meta-analysis study covering the period between 1990 and 2008, the effects of flax seed intake on the blood cholesterol profile were evaluated. 28 different studies were included in this study, and the total cholesterol and LDL cholesterol levels were found to decrease as 0.10 mmol/L (95% confidence interval- CI: -0.20, 0.00 mmol/L) and 0.08 mmol/L (95% confidence interval-CI: -0.16, 0.00 mmol/L), respectively. It was stated that the cholesterol reduction effects were more obvious in women, especially in postmenopausal women, in people with a high beginning cholesterol level (Pan, 2009) [33] .

Anti-Inflammatory Effect

In a study conducted by Caugney et al., investigations were performed on anti-inflammatory activities in patients with rheumatoid arthritis with a diet including flax seed oil. In the research on healthy volunteers, the diets with sunflower oil administration and the diets with flax seed oil administration were examined in parallel. Diets were applied to the subjects for 8 weeks, and the fish oil capsules were additionally given to the subjects at the end of the first four weeks. In the group with flax seed administration, it was discovered that the ALA and EPA values increased 3 and 2.3 times at the end of the first four weeks, respectively. At the end of 8 weeks, no increase was observed in the ALA levels, however, the EPA and DHA levels were found to continue increasing. In the group with sunflower oil administration, no increase was observed in the ALA and EPA values at the end of the 4th week, however, an increase was found in the EPA and DHA values at the end of the 8th week.

While no change was observed in the TNF-α, IL-1β, thromboxane B_2 and prostaglandin E_2 levels in the group with sunflower o il d ietary a dministration, t he T NF-α, IL-1β, thromboxane B_2 and prostaglandin E_2 values were found to decrease by 30%, 31%, 29% and 30% in the group with flax s eed o il a dministration a t t he e nd o f t he fi rst 4 weeks. It was revealed that the TNF-α value was inhibited by 77% and 70%, the IL-1β value by 81% and 78%, the thromboxane B_2 value by 48% and 52%, and finally, the prostaglandin E_2 value by 28% and 55% in the groups with the administration of flax seed oil and sunflower oil at the end of the 8th week (Caughey, 1996) [34] . Table 4

In a study executed on experimental animals, it was shown that inhibitions occurred at a certain level in the inflammation markers such as IL-6, mac-3 and vascular cell adhesion molecule as a result of the addition of 0.4 g/day of flax seed into nutrients (Dupasquier, 2007) [35] .

Pharmacodynamic Interactions:

Flax seed should be taken at least $\frac{1}{2}$ to 1 hour before other drugs since it delays enteral absorption depending on the general pharmacodynamic properties of the laxatives (EMA, 2006) [36] .

Drugs that inhibit gastrointestinal activity together with laxative mass-forming agents should be used carefully. In order to prevent gastrointestinal blockage, flax seed should be used carefully with drugs that inhibit peristaltic activity and only under the doctor's observation (EMA, 2006) [36] .

Pharmacokinetics:

There are no recognized pharmacokinetic studies on flax seed oil.

Pharmacokinetic Interactions:

There are no recognized pharmacokinetic interactions of the flax seed oil.

Side Effects and Toxicity:

Side effects:

There are no recognized side effects of the flax seed oil for its oral intake.

Intake During Pregnancy and Lactation:

Since there are no adequate studies on this topic, it should not be taken during pregnancy and lactation.

Jobs requiring attention, vehicle and machine usage:

On this topic, there are no studies investigating the effect of the flax seed oil.

Acute and Chronic Toxicity:

No acute or chronic toxicity has been reported.

4 CONCLUSION:

Almost every part of the flax plant has a commercial use, and especially flax seed has great significance for the food and nutrition sectors. Strong and durable fibers in its structure are particularly of great importance in terms of areas of use. Flax seed contains oil rich in omega-3, digestible proteins and lignans. Today, flax seed stands out among the

	Flaxseed group			Sunflower group		
	0 wk	4 wk	8 wk[2]	0 wk	4 wk	8 wk
	% of total fatty acids					
Total SFAs	42.7 ± 0.9[a]	43.1 ± 0.9[a]	42.6 ± 0.7[a]	43.0 ± 1.5[a]	43.8 ± 3.7[a]	42.7 ± 1.4[a]
18:1n−9	12.2 ± 1.6[a]	11.8 ± 0.8[a]	12.1 ± 0.9[a]	11.8 ± 0.7[a]	11.4 ± 0.7[a]	11.6 ± 0.8[a]
Total MUFAs	15.4 ± 1.8[a]	15.5 ± 1.0[a]	15.5 ± 1.0[a]	14.7 ± 0.9[a]	15.0 ± 1.0[a]	15.7 ± 2.4[a]
18:2n−6	7.5 ± 1.3[a]	7.5 ± 0.9[a,3]	8.3 ± 1.1[b,3]	7.8 ± 0.9[a]	8.7 ± 1.1[b]	9.7 ± 1.7[b]
20:4n−6	22.9 ± 1.2[a]	21.9 ± 1.2[b]	19.2 ± 1.4[c]	23.5 ± 1.0[a]	21.3 ± 2.5[b]	18.4 ± 1.8[c]
Total n−6	36.0 ± 1.8[a]	34.1 ± 1.4[b]	30.9 ± 1.7[c]	36.7 ± 1.0[a]	35.7 ± 3.3[a]	31.7 ± 2.9[b]
18:3n−3	0.1 ± 0.1[a]	0.3 ± 0.2[b,3]	0.3 ± 0.1[b,3]	0.1 ± 0.1[a]	0.1 ± 0.1[a]	0.1 ± 0.1[a]
20:5n−3	0.3 ± 0.2[a]	0.7 ± 0.2[b,3]	2.4 ± 0.7[c,3]	0.2 ± 0.2[a]	0.3 ± 0.1[a]	1.9 ± 0.6[b]
22:6n−3	2.3 ± 0.4[a]	2.2 ± 0.4[a]	3.7 ± 0.4[b]	2.5 ± 0.4[a]	2.5 ± 0.5[a]	3.8 ± 0.6[b]
Total n−3	5.8 ± 0.7[a]	7.3 ± 0.9[b,3]	11.0 ± 1.0[c,3]	5.5 ± 1.0[a]	5.5 ± 0.8[a]	10.0 ± 1.5[b]

[1] $\bar{x}$ ± SD; n = 15 for all groups. Values within a group with different superscript letters are significantly different, $P < 0.05$. SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids.
[2] n = 13.
[3] Significantly different from corresponding value in sunflower group, $P \leq 0.05$.

Table 4. fattyacid of phospholipid on mononuclearcells 0: basic line 4: the 4^{th} week of diet 8: the 8^{th}week of diet (Caughey,1996).

functional additives in the food industry due to the presence of α-linolenic acid, lignans and fibers in its content. Among the oils obtained from seeds, flax seed comes into prominence since it has high contents of α-linoleic acid (ALA, 18:3n-3) and lignans. Flax seed contains oil by 35-45%, and 45-52% of it consists of ALA. ALA is classified as omega-3 group fatty acid and has anti-inflammatory, antithrombotic and antiarrhythmic characteristics.

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