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(REVIEW ARTICLE)



# Exploring the therapeutic potential of flaxseed oil: Insights from pre-clinical and clinical research

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#### **Abstract**

Flaxseed is also known as linseed which is derived from linseed plant. This has in folk medicine been used as Fiber and oil for health benefits in health and nutrition in treating a number of diseases. Flaxseed oil contains unsaturated fatty acids such as omega-3 fatty acids, α linolenic acid (ALA), oleic acid and palmitic and stearic acid. The various uses of flaxseed oil include cardiovascular health, diabetes, weight management, cancer, digestive problems, anti-inflammatory properties, high blood pressure, hormonal imbalance, obesity, neurological disorders and others. Flaxseed oil also aids in strengthening the immune system. It has also become more popular due to its benefits to the health of individuals. Flaxseed biochemical composition includes protein (20-30%), Dietary Fibers, Lignans, and Minerals. It is used in bakery products as food ingredient flaxseed oil. Flaxseed oil can also be applied in the formulation of skin care products for moisturizing, anti-aging and skin conditions. It acts as an anti-inflammatory and has positive effects on wound healing that impacts the size of wounds on burn patients. It can also be used as a Dietary Supplement as it is a powerful supplement which can be beneficial in so many health disorders. The concentration and potential effect of flaxseed oil depend on research done on animals and humans recently and the uses in commerce. This review will summarize the preclinical and clinical studies investigating flaxseed oil and its potential uses and therapeutic effects for various diseases. Thus, the primary source of data analyzed in the present paper was the literature review based on articles that concerned the topic of flaxseed oil and its impact on the human body. Information was obtained from preclinical studies, RCTs, and meta-analyses in the peer-reviewed literature.

**Keywords:** Flaxseed oil; Health benefits; Omega-3 fatty acid; Dietary Supplement; Pre-clinical and clinical research

## 1. Introduction

Flaxseed oil is extracted from seeds of flax plant which is scientifically known as Linum usitatissimum. It has been evaluated in folk medicine the fiber and oil for some potential health benefits recovering several diseases. The main constituents of flaxseed oil are omega-3 PUFAs, especially the ALA, along with other PUFA-s such as oleic, palmitic and stearic acids. Phenols are classified in to three groups which includes the phenolic acid, flavonoids and lignans. Flaxseed oil or linseed oil is the oil extracted from flaxseeds through a process of grinding followed by pressing. Flaxseed is composed of 20-30% of protein and its major components are globulins and glutelin's. It contains bioactive peptides that can lower cardiovascular risk factors. Dietary Fibers present in Flaxseed is both soluble and insoluble fiber that helps in digestion and regulates the levels of glucose and cholesterol. Flaxseed is rich in lignans which are strong antioxidants and weak estrogen. It contains much more lignan than any other plant which may inhibit the growth of cancers especially hormone receptor positive kinds. Flaxseed contains calcium, magnesium, phosphorous, and potassium, which are crucial in the reduction of risk of heart attack and stroke.

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It has several reported actions and health benefits: Flaxseed may help decrease type 2 diabetes as the seeds contain dietary fibers, omega-3 fatty acids and lignans. Flaxseed lignan SDG has the ability to suppress glucose synthesis. It enhances overall glycaemic control through its impacts on glucose and postprandial blood glucose levels (1,2,3). Flaxseed oil might reduce the risk of lung, skin, breast and colon cancers. It can inhibit angiogenesis and hence it can prevent the growth of cancer cells in tumour. Lignans for the risk of development of cancer may be reduced by compounds such as SDG, due to its estrogenic activity and antioxidant activity. The research done on flaxseed indicated a slowing of tumour development in animals and an increase in survival of breast and prostate patients (4,5). Flaxseed oil may reduce kidney inflammation, fibrosis, and chronic kidney disease (CKD) in experimental animals. It is associated with decreased CKD incidence and lower blood pressure, a risk factor for CKD. Yet, ALA may be less potent as EPA and DHA in promoting kidney health and preventing CKD (6). Flaxseed improves cholesterol and lipid concentrations as demonstrated in animal and humans. Some research suggests it could help reduce cholesterol, although research on its effects on heart health is scarce. Flaxseed can enhance the properties of endothelium-derived relaxing factors and decrease the cardio risk, while some evidence is conflicting (7-11). Prevention and Treatment of Obesity which aids in reduction of hunger. Soluble fibers inhibit the rate at which foods are emptied from the stomach and digested in the small intestines, therefore aiding in weight loss (12). Natural Treatment of Bowel Syndrome: According to the analysis, fiber is important for the prevention and treatment of constipation. It treats irritable bowel syndrome and enhances intestinal motility. Research also indicates that they maintain impact on nutrition and gastrointestinal health (13-15). A substance that can reduce inflammation by reducing both the magnitude and duration of inflammatory reactions which is pain, redness, and swelling those results from increased blood supply, capillary permeability, and migration of leukocytes from the blood. These include lipids such as PGE2, LTB4, peptide such as IL-1 $\beta$  and TNF- $\alpha$  and reactive oxygen species. EPA and DHA also generate anti-inflammatory lipids such as resolvins and protectins which aid in reducing the migration of neutrophils and the production of mediators associated with inflammatory reactions. In the rat study conducted by Ghazavi et al., there were neuroprotective effects evident after pre-treatment with flaxseed oil and an increase in brain neurotrophic factors. Likewise, flaxseed oil also elevated the dopamine and serotonin concentrations, indicating that it might interact favorably with antidepressant medications. Also, flaxseed oil lessened depression signs in rats and showed depressant-like effects in postpartum depression models. Such analysis could be beneficial for determining the main cultivars for therapeutic flaxseed oil procurement (17-19). Omega-3 fatty acid is also important in the brain function and development. There are some indications that ALA from flaxseed oil can play a role in cognitive health, although more research is needed in this field. Skincare products made with flaxseed oil can include this additive for its ability to moisturize the skin and have anti-inflammatory effects. Probably has benefits in terms of conditions such as eczema and dry skin. These physiological effects may be due to the richness of flaxseed oil in fatty acids, phytoestrogens, and various antioxidants, as shown in the experiments conducted with ovariectomized animals.

# 2. Mechanisms of Action

- Effects on Lipid Metabolism
- Antioxidant Mechanisms
- Modulation of Inflammatory Pathways
- Impact on Cellular Apoptosis

# 2.1. Potential Risks and Side Effect-

Some people may experience gastrointestinal problems such as bloating, gas, diarrhea, or an upset stomach. Although rare, flaxseed oil can cause allergic reactions are seen in some individuals, having symptoms like rash, itching, or swelling. Flaxseed oil may have a mild blood-thinning effect due to its omega-3 content. If you're on blood-thinning medications or have a bleeding disorder. Flaxseed oil might interact with specific medications such as diabetes, blood thinners and few antidepressant medications. High doses of flaxseed oil might decrease blood pressure, so monitor your blood pressure if you have hypotension or are taking medication for hypertension.

**Recommendations for Safe Use flaxseed oil**- Start with a Small Dose, Choose High-Quality Oil, Store Properly, Consult Your Healthcare Provider, Monitor for Side Effects, Check for Interactions, Avoid Heating.

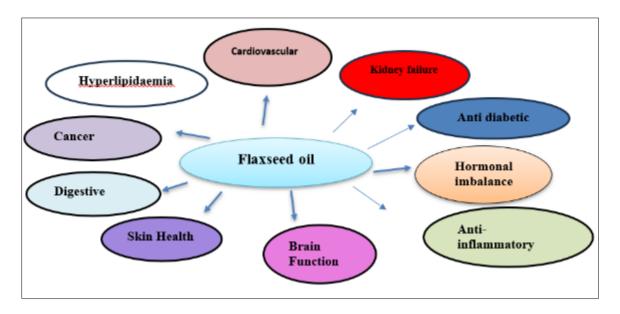


Figure 1 Health benefits of flaxseed oil

 $\textbf{Table 1} \ \textbf{Role of flaxseed oil in various pre-clinical models}$ 

S.n o	Activity	Animals	Study perio d	Induced	Parameter assessed	Outcome	References
1	Hormonal imbalance	adult female SD rats, aged 6 months	8 wee ks	bilateral ovariectomy (OVX) and sham operations were performed under anesthesia using a mixture of ketamine (10%) and xylazine (2%).	Antioxidant, Biochemical Parameters- Alkaline phosphate, calcium, oestrogen and progesterone levels. Stereological study- uterus weight, perimeter and myometer ovarian, endometrial thickness, vessel ovarian diameter and lumen volume. Histopathology study, Statistical analysis.	Flaxseed oil mimic the oestrogen hormone in female and can be likely used in treatment of hormonal replace therapy (HRT).	Tanideh R et al 2021 [20]
		Female SD rats, aged 6 weeks	8 wee ks		Vaginal smear, blood sex steroid hormones, lipid, insulin resistance, plasma and ovarian inflammation, intestinal/vaginal microbiota, Histopathology study, Statistical analysis.	Dietary flaxseed oil improves PCOS through sex steroid hormone, intestinal /vaginal microbiota-inflammation and can be	Wang T et al 2020[21]

						consumed by the vegetarians.	
2	Skin	Male NC/Nga mice, aged 6- week-old	3 weeks	Mice were shaved, and 1 mL of 5% sodium dodecyl sulphate (SDS) was applied to their backs 20 times using a cotton swab to remove the lipid lamella from the stratum corneum.	Histochemistry, immunohistochem istry, Expression of Fc receptors, β-Hexosaminidase, Nitric oxide assay, Western blot analysis, RT-PCR, Data analysis.	Flaxseed oil reduce the symptoms of Atopic dermatitis which includes epithelial damage, pruritus, redness and swelling regaining skin barrier and reduce inflammation.	Yang J et al 2017[22]
3	Hyperlipidae mia	Male rats, aged 8 week	21 days	High-fat diet (HFD) which include daily diet of 10% vegetable oil and 10% tail oil.	Lipid parameters: cholesterol, TG, HDL, LDL, VLDL.	Flax seed oil reduce biochemical parameters.	Shahidi S et al 2022[23]
4	Kidney failure	Male rats (Rattus norvegicu s)	6 weeks	Thioacetamide induced renal toxicity.	Biochemical parameter: creatinine, BUN, uric acid. Histopathology study	Kidney damage is guarded may be due to possible antioxidant properties present in flaxseed oil.	Shaikh Omar AM et al 2018 [24]
		Adult male albino rats.	5 weeks	the rats were given diclofenac Sodium by injection a dosage of (100 mg/kg) for 72 hours.	Biochemical parameter: haematological, Glucose, Total protein, Albumin, Urea, Uric acid and Creatinine organ weight, ALT and AST, Na, K, Ca, Histopathology study, Statistical analysis.	10% flaxseed oil showed better function in kidney, it may be used in food items as of its benefits in health.	SM, A et al 2022[25]
5	Anti metabolic syndrome	Mice	6 weeks	Mice induced with alcohol	AST and ALT levels, endotoxin, gut microbiota, Histopathology study, Statistical analysis.	Flax seed oil is used in prevention and treatment of ALA by enhancing alcoholic liver disease through regulating gut microflora and anti-	Zhang X et al 2017[26]

						inflammation properties.	
		Male albino rats (SD Strain)	4 weeks	D- galatosamine- sensitized Male albino rats	Urinary 8-hyroxy deoxyguanosine, immunohistochem istry, Statistical analysis.	Flaxseed oil shields the liver from damage by reducing inflammation and oxidative stress.	Hussein, J et al 2016[27]
		Male apoE-KO mice aged 4 weeks	12 weeks	A mice is given Western-type diet (WTD) induced non-alcoholic fatty liver disease (NAFLD).	Lipid parameters: cholesterol, HDL, LDL, VLDL, ROS, oxidative stress, biomarkers of liver injury, inflammatory cytokines, RT-PCR, Western blot, Histopathology study, Statistical analysis.	Flaxseed oil decreased the oxidative stress and inflammation improve the NAFLD Progress.	Han H et al 2017[28]
		piglets male	21 days		AST and ALT, AKP and glutamyl transpeptidase (GGT) levels, hepatic fatty acid, mRNA RT-OCR, Western blot, Histopathology study, Statistical analysis.	The findings indicate that flaxseed oil suppresses necroptotic and inflammatory signalling pathways, thereby safeguarding the liver from damage associated with inflammation.	Wang, L et al 2018 [29]
6	Anti diabetic	Male SD rats	8 weeks	Stz induced diabetes	Biochemical parameter, evaluation in brain monoamines, nitric oxide and MDA, Statistical analysis.	Flaxseed oil may assist in dysfunction treatment of brain in diabetic condition through enhancing neurotransmitt er.	Badawy, E.A 2015.[30]
7	Brain	Male Wistar rats	3 weeks	The diet containing ammonium was prepared by mixing dry rodent food with 20% w/w ammonium acetate.	Behaviour test, open field test, Barnes maze, spontaneous object recognition test, rotarod, histology, Statistical analysis.	Flaxseed oil orally administered avoid motor and cognitive problems along with neuronal changes in rats with hyperammonae mia. It is useful	Ocaña- Sánchez MF et al 2023[31]

					in liver associated brain problems (hepatic encephalopathy ).	
	baby rats		toxicated group and received an intraperitonea l injection of aluminum chloride (AlCl3) twice a week (75 mg kg b.wt.) over a period of 30 days before Female intoxicated rats with aluminium chloride injections for 30 days Twice weekly	Protein estimation, antioxidant activity, lipid peroxidation, nitric oxide and MDA, acetylcholinesteras e, lipid extraction, Behaviour test, Statistical analysis.	Flaxseed oil have neuroprotective action in growing rats brain in young rats which neutralises the effect of aluminium chloride through antioxidant and antinflammatory effect. Enhance fatty acid in brain and behaviour.	LOUNIS, W et al 2023[32]
	Wistar rats	4 weeks	rats were given the cadmium induced Neurotoxicity	Behaviour test, Novel object recognition test, Morris water maze, Biochemical parameter: glutathione, MDA, nitrite, acetylcholinesteras e, protein, apoptosis, Histopathology study, Statistical analysis.	Flaxseed oil have beneficial impacts on brain. It also has enhanced GSH levels and cell death is reduced, whereas Minimizing NO, AChE, and MDA levels. Its decrease neuron injury, has adapted by tissue analysis.	Mishra, D.K et al 2020[33]
	Male SD rats, aged 2 months.	28 days	Rats were anesthetized then the left sciatic nerve was exposed and compressed for 10 seconds.	Walking track, toe spreading reflex, sciatic nerve isolation, transmission electron microscopy, Statistical analysis.	Flaxseed oil enhance recovery of injured sciatic nerve and myelin thickness increased; nerve regeneration is showed.	Che Ramli, M.D et al 2020[34]

		Male Wistar albino rats	6 weeks	Monosodium glutamate ind uced brain injury.	Biochemical estimation: ALT and AST, urea and creatinine. Lipid peroxidation, Paraoxons 1 activity, neurotransmitters in blood, blood fatty acids by HPLC, Statistical analysis.	Flaxseed oil improve brain cells which was affected with MSG.	Youness, E.R et al 2019[35]
8	Anti inflammator y	Adult Male Wistar rats	6 weeks	Induction of periodontitis Periodontitis was induced by ligature placement under general anaesthesia.	RT-PCR, qpcr: IL- 10, TGF $\beta$ 1, Osteopontin, $\beta$ - actin, Histopathology study, Statistical analysis.	Flaxseed oil reduce the inflammation and quickens healing in the gum tissue Which was mechanically damaged.	Abu El- Azayam et al 2023[36]
		Male SD rats	6 weeks	DSS (dextran sulphate sodium) induced.	Disease activity index assesses the seriousness of ulcerative colitis, Microbial analysis of the cecal content, oxidative: SOD,GSH , MPO and MDA, Histopathology study, Statistical analysis.	Flaxseed oil decrease inflammation and intestine damage in colitis of rats. This can be due to antioxidants, gut bacteria and inflammation.	Zhou, Q et al 2020[37]
		5 beagles and 5 greyhoun ds, female dogs.	21 days		White blood cell harvest and RNA extraction, PCR, Plasma fatty acid, Statistical analysis.	Flaxseed oil have ALA which changed inflammation-related genes are expressed in white blood cells.	Purushotha man, D et al 2014[38]
9	Cancer	invitro	4-6 Days	B16-BL6, MCF-7, MDA-MB-231, MDA-MB-468, HeLa, HEK293, HSG and HBL-100 maintained in medium  DMEM with added fetal bovine serum & antibiotics.	Trypan blue cell, Flow cytometry, Methyl tetrazolium blue viability assay, Fluorescence microscopy, Immunoblot analysis, Caspase activity, Statistical analysis.	Flaxseed oil indicate inhibition growth of cancer cell and apoptosis was seen in few cancer cells.	Buckner, A.L et al 2019[39]

i	nvitro		KB cells, oral cancer cell lines.	Cell viability assay, Cytotoxicity assay by neutral red incorporation, Statistical analysis.	Flaxseed oil might help to fight the cancer.	Reethega, V et al 2018.[40]
i	nvitro		Two Brest cancer cell lines, MCF7 and MDA-MB231	Apoptosis detection, cell cycle, H2AX and PI3K Pathways, lipid peroxidation, gene expression, protein extraction, cell signalling, RT-qPCR, Statistical analysis.	Phenolic extract from the flaxseed oil has reduce breast cancer. The extract reduce growth and increase cell death in MCF7 cells. Slight effect on MDA-MB231 cells.	Sorice, A et al 2016.[41]
C	Male C57BL/6 Mice	40 days	Mice were challenged with 2x105 /100 μl murine B10 melanoma.	Enzymic antioxidant, Glutathione, Oxidative stress marker and cytokine assay, Statistical analysis.	Flaxseed oil will stop the spread of lung cancer. improve enzyme levels and antioxidant in blood. The markers like metastatic lesions.	Han, J et al 2015.[42]
	Male Wistar rat	15 days		Vascular reactivity and 02, Western blot, C reactive protein, Statistical analysis.	Flaxseed oil will increase vascular reactivity to phenylephrine by enhancing ROS production and COX-2.	Nunes, D.O et al 2014.[43]

 Table 2 Role of flaxseed oil in various clinical models

S.no	Activity	Dose	Design	Conclusion	References
1	Constipation	flaxseed oil and Olive oil compared to mineral oil.  4 mL/day oil was started and during monitor period's adjustment was done.	Randomization, Double blind, controlled trials was done. constipated patients included 29% males, age 51± 12.	The Rome III score showed significant improvement in patients receiving mineral oil ( $10.5 \pm 5.0$ to $4.1 \pm 4.0$ ; P < .01), olive oil ( $10.3 \pm 4.2$ to $3.2 \pm 3.8$ ; P = .01), and flaxseed oil ( $9.6 \pm 4.2$ to $6.0 \pm 5.1$ ; P < .01). Use of olive oil or flaxseed oil was as effective as mineral oil constipation in	Ramos, C.I et al 2015. [44]

				patients receiving	
2	Metabolic syndrome	flaxseed oil and sunflower oil 25 mL/day.	Randomized controlled trials, using the block method. 3-week washout period. 30–60 age. exclusion criteria is chronic diseases such as autoimmune or inflammatory diseases, cancer, kidney and liver problems, blood pressure, diabetic medications, nutraceutical with omega-3 fatty acid, using aspirin, propranolol, anti-inflammatory drugs, history of hospitalization for surgery, pregnant and breastfeeding.	haemodialysis.  Flaxseed oil may manage or reduce inflammation in patients with metabolic syndrome, which will lead to heart and diabetes complication. The study did not find any significant changes in antioxidant levels or blood clotting.	Akrami, A et al 2020. [45]
		Flaxseed oil and sunflower oil 20 ml/d.	Randomization, Double blind, placebo-controlled trials was done.  NAFLD patients inclusion criteria are age eighteen years, BMI of 25 kg/m2.  Diabetes Patients, organ failure, cancer and malnutrition, special diets, medications that affect BP, lipid profile and fatty liver, alcohol were not included. Exclusion criteria is consumption of fish oil supplements, infection or inflammatory disease.	NAFLD patients who were on low-calorie diet and moderate exercise having flaxseed oil had good results in liver fat, weight, and inflammation compared to using sunflower oil. Both groups had weight loss and had similar reductions in liver enzyme levels, waist size, and blood pressure. Flaxseed oil might be effective in more serious liver problems and high liver enzyme levels.	Rezaei, S et al 2020. [46]
3	Prediabetes	Flaxseed oil, placebo containing(2000-mg) 2 times a day. 14 weeks	Randomization, Double blind done with overweight prediabetic patients aged 30-48 years. fasting blood glucose 100-125 mg/dl included. Exclusion criteria receiving hypoglycaemic oral medications, acute and chronic disease, smoking, special diet, amenorrhea, taking antiinflammatory medications, consuming fish oil supplement, taking fish and using soybean.	There were no notable Modifications in fasting blood glucose levels, and the intervention did not Boost inflammation or body composition in individuals with overweight prediabetes.	Shareghfarid, E et al 2022. [47]
4	Anti inflammatory	Flaxseed oil and olive oil 30g of oils for three weeks	Randomization, Double blind, parallel group trial. inclusion criteria were Burn covering 20-50% of the body. Thermal or chemical burns. Hospitalized in 24 hours of the	According to the results, the combination of oils effectively reduced inflammation and improve in wound	Ghanbari, A et al 2023. [48]

			burn. Aged fifteen-sixty-five years. BMI between eighteen and thirty. Able to eat and drink normally. Willing to participate in the study.  Exclusion Criteria:  Kidney or liver failure. Diabetes. Malnutrition when admitted. History of Allergic reaction to olive or flaxseed oil. Used fatty acids in the past month. Needs special nutritional support or mechanical ventilation. Top of Form  Bottom of Form  patients with total burn surface area (TBSA) ranging for 20-50%	healing, demonstrating Beneficial effects on wound size in burn patients.	
		Flaxseed oil and olive oil 15 ml for 6 weeks	Researchers tracked diet, body weight, and physical activity at the start and end. They measured blood markers for inflammation and other health indicators. To ensure participants followed the oil regimen, they checked the fatty acids in their red blood cells. The effects of treatment was analysed using statistical methods.	Consumption of flaxseed oil didn't have any effect in inflammation or blood markers for healthy young adults who use olive oil in their usual diet.	Kontogianni, M.D et al 2013. [49]
5	Brain	Flaxseed oil 2.2 grams	Randomization, Double blind, placebo-controlled trials. Eligibility Criteria Age: 65-80, Right-handedness. Exclusion Criteria disorder related to cranial nerve, Participants with serious visual or hearing impairment, Intensely overweight/underweight, Frequent fish consumers, Participants having psychiatric symptoms that that hinder their Capability to engage in study.	It improved verbal proficiency in healthy older adults. Verbal fluency helps with cognitive health and can predict Alzheimer's disease.	Ogawa, T et al 2023. [50]
		1000 mg capsule, contains flaxseed oil twice daily for10 weeks.	Randomization, Double blind, controlled trials Subjects are depressed women aged 18–45 Inclusion Criteria:  Women aged 18 to 45, Diagnosed with depression (according to DSM-IV), Taking antidepressant medications  Exclusion Criteria:	taking flaxseed oil, taken increased serum BDNF levels and improved depression in women. This suggests that dietary factors like flaxseed oil help to manage depression. More	Poorbaferani, F et al 2020. [51]

History of heart, kidney or liver problems, hypertension, diabetic or cancer. Any type of breast or ovarian cysts in the patient or her family. smoking or addiction, Pregnancy or breastfeeding, Use of alcohol, herbal drugs, or any other	groups and longer- term follow-ups is needed to confirm	
<u>o</u> .		

## 3. Future Directions in Flaxseed Oil Research

Flaxseed oil is having numerous health benefits, further research is needed to Interpret how different extraction methods can affect its composition and effectiveness. Studies should find the chemical variations among flaxseed effects and varieties in both animal and human trials, particularly focusing on potential neuroprotective properties for conditions like Alzheimer's disease. Flaxseed oil may also treat ulcerative colitis and certainly can be combined with other therapies for cancer management. Future studies must focus on the interactions between flaxseed oil and cancer treatments. Further research is recommended to impose the benefits of flaxseed oil in patients with severe NAFLD or non-alcoholic steatohepatitis. Development of skincare formulations using flaxseed oil and mucilage Additionally, future research should explore how flaxseed oil interacts with other natural extracts, enhance understanding of its stability, and develop new formulations for improved use in pharmaceuticals and nutraceuticals. Gaps in Current Knowledge: Long-Term Safety, Mechanisms of Action, Optimal Dosage and Formulation, Interactions with Medications, Impact on Gut Microbiome

### 4. Conclusion

In conclusion, flaxseed oil has various health benefits such as reducing the risk of cardiovascular disease, diabetes, cancer, and obesity. It also has anti-inflammatory properties and boosts the immune system. Flaxseed oil is rich in omega-3 fatty acids, proteins, dietary Fibers, lignans, and minerals. It has been used in food products and skincare due to its health benefits. Research shows that flaxseed oil can have positive effects on hormonal balance, skin health, kidney function, obesity, bowel syndrome, inflammation, and neurological disorders. However, there are potential risks and side effects to consider, such as gastrointestinal problems and interactions with medications. Future research should focus on the long-term safety, optimal dosage, mechanisms of action, and interactions with medications of flaxseed oil. Their ability to enhance nutrient profiles and improve dietary choices makes them a valuable component of functional foods and nutraceuticals.

## Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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