Review Paper

The Mechanism of Action and Potential Impact of Flaxseed on Gastrointestinal Manifestations in Cystic Fibrosis: A Narrative Review

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ABSTRACT

Background: Cystic fibrosis (CF) is an inherited disease, which leads to death at a young age. No definite treatment has yet been found for CF. Therefore, it is important to find new therapeutic and medicinal approaches for CF. Flaxseed is an antioxidant dietary and anti-inflammatory supplement with a high omega-3 fatty acid content.

Objectives: In this article, the mechanism of action of flaxseed as a novel supplemental treatment for CF is discussed.

Methods: In this review, we searched Iranian traditional medicine (ITM) sources, such as Zakhire Kharazmshahi and Canon of Medicine. Then, from inception to October 2020, data sources, including Google Scholar and PubMed in the English language were comprehensively explored for the mechanism of action of this herbal remedy on CF.

Results: Flaxseed may possess effects on CF gastrointestinal disorders due to its properties, including consumer acceptance as a functional food, being the best non-animal reservoir of omega 3 fatty acid, alpha-linolenic acid (ALA), and soluble fiber, as well as its anti-inflammatory and antibacterial effects with modulating intestinal microbiota.

Conclusions: Regarding the mentioned potential mechanisms of action, it could be hypothesized that flaxseed can be served as a novel medicine for CF.

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1. Context

The cystic fibrosis transmembrane conductance regulator (CFTR) protein deficiency causes cystic fibrosis (CF), which is an autosomal recessive disease and is one of the most frequent lethal genetic disorders in Caucasian people (1). CFTR regulates salt and water transepithelial transport in numerous duct epithelial surfaces (2). One in every 2000-3000 live newborns is diagnosed with CF. Reduced transepithelial Cl secretion and an imbalance in water and epithelial electrolyte homeostasis are caused by CFTR failure (3-5). In patients, serious issues in several tissues, including exocrine pancreatic dysfunction and intestinal blockage resulting in the absence of CFTR protein and/or its dysfunction (6, 7). The digestive complications in CF are due to the production of thick and sticky mucus due to impaired transfer of water and chloride, which leads to obstruction of the ducts and prevents the release of digestive enzymes into the intestine. Therefore, the digestion and absorption of food are impaired in CF (8). Insufficiency in pancreatic enzymes leads to malabsorption and maldigestion of fat, fat-soluble vitamins, and protein (9). A key component of challenging standard clinical care is fat malabsorption therapy to optimize the nutritional status and growth of patients with pancreatic insufficiency, like CF (10). So to reduce the CF complications in patients, such as failure to thrive, pancreatic enzyme replacement therapy (PERT) and optimization of nutritional deficiencies have been used. Also, these parts of CF treatment can improve chronic lung disease and quality of life (9). Also, anti-inflammatory medications, including corticosteroids, ibuprofen, macrolides, antioxidants, and anti-proteinases have been proposed for CF for about the last two decades (11).

Because of the intricacy of the medication regimen in chronic illnesses, patients only comply with approximately half of their treatments. Therefore, therapeutic objectives and patients' lifestyles must be adjusted (12). Health care practitioners have considered the use of complementary and conventional medicine to lessen the signs of CF in recent years, and roughly 66% of CF patients have utilized one of the alternatives or supplementary techniques (13).

Complementary and traditional medicines are the origins of new and usually natural medications. Iranian Traditional Medicine (ITM) is one of the oldest and most valuable traditional medicine (14, 15). ITM history goes back thousands of years ago (16). Iranian Muslim physicians, like Avicenna (980–1037AD), and many others in the early medieval had an effective role in the flourishment of ITM (17, 18). Numerous manuscripts by these physicians, including the Canon by Avicenna, were used as a textbook in western and eastern Universities until the four last centuries (14). These important manuscripts were written and practiced in Iran till the three last centuries and various Iranian physicians supported the subjects or drugs mentioned in these books from the 10th to the 18th century with at least 800 years by testing and examination (19).

Knowing that nutritional supplements with anti-inflammatory effects have an important role in CF therapeutics as an adjunctive therapy. In this study, we attempted to introduce flaxseed, an Iranian traditional herbal medication, as a supplemental therapy for CF. In various Iranian medieval medical writings, this herbal medication is often referenced. Possible mechanisms and functions of flaxseed in CF were also investigated in this study.

2. Materials and Methods

The purpose of this review was to look at the impact of flaxseed on gastrointestinal signs induced by sticky and thick secretions in CF patients' gastrointestinal ducts. ITM sources, such as Zakhire Kharazmshahi and Canon of Medicine were used to find relevant data, while data sources, like Google Scholar and PubMed, were searched without time constraints from conception to October 2020 using a mix of keywords, such as CFTR, cystic fibrosis, alpha-linolenic acid, flavonoids, omega-3, functional food, and gut microbiota. Flaxseed was investigated to determine the mechanism for action potentials of flaxseed on CF.

3. Results

Flaxseed is approved to treat colon damage from laxative misuse, chronic constipation, diverticulitis, and irritable colon by the German Commission E. It is also used as a mucilage in the treatment of gastritis and enteritis. It is allowed for use as a local inflammatory poultice when applied externally (20). Also, flaxseed is a beneficial medicinal herb for the gastrointestinal tract and respiratory system according to its pharmacological effects, which were mentioned in ITM sources (Table 1) (21, 22).

Cystic Fibrosis in Iranian Traditional Medicine

Although CF is not addressed in ITM sources, it is categorized as a disease caused by the formation of viscous

Table 1. Pharmacological effects of flaxseed on the gastrointestinal tract and respiratory system according to ITM sources

The Human Body System	Flaxseed Effects
Gastrointestinal tract	Relieving inflammation of the stomach and intestines Relieving pain and ulcers of the gastrointestinal tract Laxative effect as well as the cessation of diarrhea Anti-inflammatory effects on the liver
Respiratory system	Clearance and separation of the sticky mucus Bronchodilation Clearing airways sputum more easily Effective on rhinitis and sinusitis

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secretions in the bodily ducts. We discussed flaxseed as a single herb indicated by ITM for the treatment of sticky, thick airway secretions and its benefits based on the current research. In ITM publications, flaxseed is the most often prescribed herb for various illnesses (22, 23). Flax (Linum usitassimum) belongs to the Linaceae family (24). Almost all parts of the flaxseed are used for various purposes (25, 26). The use of flaxseed has been common among people since ancient times (27). Today, in more than 50 countries, mostly in the Northern hemisphere, flaxseed is cultivated (28). Protein, fat, insoluble and soluble fibers, phenolic substances, linatine, trypsin inhibitor, lignans (phytoestrogens), vitamins, minerals, and selenium can be found in flaxseed (29). Flaxseed has anti-inflammatory properties as well (30-35). Flaxseed has been shown to slow the development of atherosclerosis (36-38), lower blood sugar in type 2 diabetics (39, 40), change the bacterial ecology in the intestines of animals (41, 42), and has anti-cancer properties (43, 44).

Flaxseed is described in traditional Iranian literature and is commonly utilized in ITM as a therapy for sticky and thick secretions (22). In this review, we tried to introduce the potential effect of flaxseed on the polyunsaturated fatty acids (PUFAs) malabsorption in CF patients.

Expected mechanisms of action of flaxseed in CF gastrointestinal manifestation

Based on the main physiopathological opinions about CF, it seems that flaxseed can be a hypothetical choice for the development of herbal complementary medicine to manage gastrointestinal disorders due to CF. The reasons for this hypothesis are as follows:

Flaxseed is increasingly welcomed by consumers as a functional food (28, 45). It is a good reservoir of alpha-linolenic acid (ALA) (28, 46) and omega-3 fatty acids (25, 26, 47). The amount of ALA in flaxseed is about 55% and ALA is one of the active biological components in flaxseed, which nutritionists and medical researchers are interested in it due to its potential health benefits (48). Flaxseed also includes roughly 30% of fibers in food, one-third of which are soluble viscous fibers (mucilage) (49). Increased fiber intake to 30g per day with additional water may alleviate gastrointestinal symptoms in certain persons with recurrent abdominal pain and increase energy intake and appetite in many patients on the CF diet, which is generally low in fiber (50).

Flaxseed as a functional food

Nutritional deficiency remains a big concern in CF patients. The CFTR mutation causes nutritional deficiencies by causing the development of excessively sticky and thick mucus, which interferes with the digestion and absorption of nutrients, particularly fat-soluble vitamins and fat, and prevents the entry of digestive enzymes into the intestine. Therefore, food is not digested or absorbed properly in CF, resulting in maldigestion and malabsorption. Bacterial overgrowth, intestinal inflammation, exocrine pancreatic insufficiency, dysfunction of enteric circular muscle, and bicarbonate and bile acid secretion impairment are known as associated complications in CF patients (8). The essential fatty acid (EFA) abnormal metabolism is a current issue in CF patients (51) and they have fewer EFAs in their plasma than the normal control group (52). Accordingly, omega-3 fatty acid supplementation shows effective therapeutic effects (53). More than ten studies have evaluated the potential and clinical benefits of omega-3 fatty acid supplements in CF (52). Therefore, a necessary part of multidisciplinary care for CF patients is nutritional management. Despite ongoing nutritional disputes from diagnosis, the principal goals of nutritional management are to ensure normal growth, and development and to produce and maintain the intake of high-quality nutrition throughout life (54-56).

Plant-based foods are especially considered a simple way to incorporate the conceptions of health via natural products into our diet (57). Requisition for medicinal plants is increasing due to a growing recognition that most natural products have no side effects, are non-toxic, and are easily available at a low price. Medicinal plants are also rich in antioxidant compounds, which are known to help the human body defend against many disorders, inflammatory conditions, digestive complications, arthritis, and diabetes. Due to the growing burden of these diseases, it becomes more essential than ever to survey the use of nutritionally-rich natural foods in the development of generally consumed functional foods (58). Various definitions exist for functional foods as follows: 1. 'Healthful products, consisting of modified food or ingredient that may supply health benefits over traditional ingredients' (59), 2. 'Foods that possess physiologically active compounds and thus, supply a health benefit over basic nutrition' (60).

The importance of flaxseed as a functional food in the world's food chain is being established (45). Due to its potential health profits and great nutritional profile, flaxseed has become a significant ingredient in diets, particularly designed for special health benefits (28). Also, flaxseed according to the previously mentioned in this essay is a good source of ALA as a part of PUFA; thus, it seems that flaxseed could be used as a functional food for EFA disorder in CF patients.

Flaxseed and gut microbiome-dependent malnutrition

Microbes in the gastrointestinal tract (for example, gut microbiota) work with the human host to perform a number of functions that the host alone cannot perform. Although it is incompletely understood, the gut microbiota is involved in a variety of host functions, including intestinal function and development, drug metabolism, and micronutrient synthesis. Also, gut microbiota plays an important role in harvesting, storing, and consuming energy obtained from the diet (61). Recently published studies have shown that human diseases, including CF, are associated with gut microbiota. In addition, chronic inflammation of the intestine, even in the absence of gastrointestinal symptoms, is present in most CF patients. Although there are studies on the relationship between inflammation and gut microbiota composition in CF, only one study showed that there is a relation between gut microbiota and intestinal inflammation in CF that suggests the key role of the intestinal-pulmonary axis in the CF evolution (62). Thus, in this part of the essay, we hypothesized that flaxseed with its anti-inflammatory effects could be a beneficial herb for malnutrition due to gut inflammation in CF.

According to one research, barley skin and flaxseed supplements in the diet of developing pigs affected the gastrointestinal microbiome's growth, composition, and function, depending on the physicochemical qualities of the source of dietary fiber and the intestinal segment (63). One study showed that extra virgin olive and flaxseed oils could affect intestinal microbiota, increase intestinal immunity, and help maintain metabolic health in mice (64). One study found that flaxseed had anti-inflammatory, antibacterial, and antispasmodic effects through a variety of pathways that could offer promising potential for the treatment of inflammatory bowel disease (IBD) (65). One study found that daily consumption of flaxseed mucilage for six weeks could improve insulin sensitivity and intestinal microbiota in obese individuals (49). Also, flaxseed oil inhibited prostaglandin E2 (PGE2) (30). PGE2 inhibits macrophage, neutrophil, and Th1 function and enhances Th2, Th17, and T regulatory responses (35). As a result, flaxseed oil has the potential to modulate immunological responses. Flaxseed oil also reduces inflammation caused by arachidonic acid (AA) by decreasing the inhibitory capacity of both lipoxygenase and cyclooxygenase, which are involved in the metabolism of AA (30).

Flaxseed and omega-3

For normal growth and function in the human body, PUFA, linoleic acid (LA) (n-6 or, 18:2 omega-6), and alpha-linolenic acid (ALA) (n-3 or, 18:3 omega-3) are necessary and should be obtained from a dietary source. Omega-3 fatty acids have been found to play a crucial role in membrane integrity and anti-inflammatory response. Some of the benefits of omega-3 fatty acids in inflammatory diseases and the fabrication of AA from LA, consisting of docosahexaenoic (DHA) and eicosapentaenoic (EPA) acids, include lowering the production of proinflammatory metabolites from the omega-six fatty acid family and enhancing the biologically less-active omega-3 end products. The exact mechanism of reduced LA levels in CF is unknown. The enhancement of the omega-six fatty acid pathway's metabolism has been identified as a possible mechanism (52, 53).

All dietitians recommend including an omega-3 fatty acid source in the diet, and flaxseed is the ideal omega-3 fatty acid source for those who do not consume fish (25, 26). ALA is a key component of flaxseed, which is an important source of omega-3 fatty acids in vegetarian diets (25, 26, 47). It is also one of the most important

PUFAs (66). Flaxseed oil has six times the quantity of omega-3 found in fish oil. Much clinical research has shown a link between oral PUFAs and anti-inflammatory actions in the body. Oral delivery of omega-3 fatty acids, such as DHA, ALA, and EPA from fish oil or flaxseed oil, suppresses the production of pro-inflammatory eicosanoids and cytokines, including IL-1b, TNF-a, prostaglandin E2, and thromboxane B2 (67).

3. Conclusions

CF is one of the most common lethal diseases among Caucasians. The buildup of abnormally thick mucus due to impaired chloride and water transport due to CFTR mutation caused digestive problems in CF patients. Digestive enzymes are prevented from entering the intestine due to the effect of the thick and sticky mucus on obstructing the gastrointestinal ducts. This consequently results in impaired digestion and absorption of food, especially fat, fat-soluble vitamins, and omega-3. Therefore, nutritional deficiency may occur in these patients. The herbal substance, flaxseed, presented in this study for the complementary management of CF is supported by classical Iranian traditional texts as well as recent investigations. Although there are no specific in-vitro studies about the effect of flaxseed on CFTR, according to the research stated, flaxseed is a functional food suggested for the treatment of disorders with excessive sticky and thick secretions. This review presented some of the ingredients of this herb and also its effects on CF nutritional deficiency due to its potential nutritional value as the best reservoir of omega-3 fatty acid to non-fish eaters, and a good reservoir for ALA as a part of PUFA; thus, it seems that flaxseed could be used as a functional food for EFA disorder in CF patients. Also, by reducing the inhibitory capability of both lipoxygenase and cyclooxygenase in AA metabolism, it exerts anti-inflammatory actions by inhibiting PGE2 and AA-induced inflammation indicating this medicinal herb as a potential anti-inflammatory herb that could be a beneficial agent for malnutrition due to CF gut inflammation and gastrointestinal microbiome dysbiosis. This functional food may be a good complement and alternative to traditional drugs with fewer side effects. To develop standard pharmaceuticals as supplemental and alternative therapies for CF, systematic validation studies are required. Some of the components found in this plant seem to be useful in the development of novel medications.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contributions

All authors contributed proportionately to this work.

Conflicts of interest

The authors declared no conflict of interest.

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References:

1. Sibley CD, Rabin H, Surette MG. Cystic fibrosis: A polymicrobial infectious disease. Future Microbiology. 2006;1(1):53-61. [DOI:10.2217/17460913.1.1.53] [PMID]

2. Li C, Naren AP. CFTR chloride channel in the apical compartments: Spatiotemporal coupling to its interacting partners. Integrative Biology: Quantitative Biosciences from Nano to Macro. 2010; 2(4):161-77. [DOI:10.1039/b924455g] [PMID] [PMCID]

3. Hamosh A, FitzSimmons SC, Macek M Jr., Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. Journal of Pediatrics. 1998; 132(2):255-9. [DOI:10.1016/S0022-3476(98)70441-X] [PMID]

4. Grasemann H, Gonska T, Avolio J, Klingel M, Tullis E, Ratjen F. Effect of ivacaftor therapy on exhaled nitric oxide in patients with cystic fibrosis. Journal of Cystic Fibrosis. 2015; 14(6): 727-32. [DOI:10.1016/j.jcf.2015.07.001] [PMID]

5. Ratjen F, Döring G. Cystic fibrosis. The Lancet. 2003; 361(9358):681-9. [DOI:10.1016/S0140-6736(03)12567-6]

6. Dey I, Shah K, Bradbury NA. Natural compounds as therapeutic agents in the treatment cystic fibrosis. Journal

of Genetic Syndromes & Gene Therapy. 2016; 7(1):284. [DOI:10.4172/2157-7412.1000284] [PMID] [PMCID]

7. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. Science. 1989; 245(4922):1066-73. [DOI:10.1126/science.2475911] [PMID]

8. Sirinupong N, Yang Z. Bioactive food components as dietary intervention for cystic fibrosis. Current Drug Targets. 2015; 16(9):988-92. [DOI:10.2174/1389450115666141122211111] [PMID]

9. Sabharwal S. Gastrointestinal manifestations of cystic fibrosis. Gastroenterol Hepatol. 2016; 12:43-7. [PMID] [PMCID]

10. Stallings VA, Tindall AM, Mascarenhas MR, Maqbool A, Schall JI. Improved residual fat malabsorption and growth in children with cystic fibrosis treated with a novel oral structured lipid supplement: A randomized controlled trial. PLoS One. 2020; 15(9):e0239642. [DOI:10.1371/journal.pone.0239642] [PMID] [PMCID]

11. Panchaud A, Sauty A, Kernen Y, Decosterd LA, Buclin T, Boulat, et al. Biological effects of a dietary omega-3 polyunsaturated fatty acids supplementation in cystic fibrosis patients: A randomized, crossover placebo-controlled trial. Clinical Nutrition. 2006; 25(3):418-27. [DOI:10.1016/j.clnu.2005.10.011] [PMID]

12. Conway SP, Pond MN, Hamnett T, Watson A. Compliance with treatment in adult patients with cystic fibrosis. Thorax. 1996; 51(1):29-33. [DOI:10.1136/thx.51.1.29] [PMID] [PMCID]

13. Stern RC, Canda ER, Doershuk CF. Use of nonmedical treatment by cystic fibrosis patients. Journal Adolescent Health. 1992; 13(7):612-5. [DOI:10.1016/1054-139X(92)90376-M]

14. Zargaran A, Zarshenas MM, Karimi A, Yarmohammadi H, Borhani-Haghighi A. Management of stroke as described by Ibn Sina (Avicenna) in the canon of medicine. International Journal of Cardiology. 2013; 169(4):233-7. [DOI:10.1016/j.ijcard.2013.08.115] [PMID]

15. Zargaran A, Zarshenas MM, Mehdizadeh A, Mohagheghzadeh A. Management of tremor in medieval Persia. Journal of The History of The Neurosciences. 2013; 22(1):53-61. [DOI:10.1080/0964704X.2012.670475] [PMID]

16. Zargaran A, Fazelzadeh A, Mohagheghzadeh A. Surgeons and surgery from ancient Persia (5,000 years of surgical history). World Journal of Surgery. 2013; 37(8):2002-4. [DOI:10.1007/s00268-013-2055-0] [PMID]

17. Golzari SE, Khan ZH, Ghabili K, Hosseinzadeh H, Soleimanpour H, Azarfarin R, et al. Contributions of medieval Islamic physicians to the history of tracheostomy. Anesthesia and Analgesia. 2013; 116(5):1123-32. [DOI:10.1213/ANE.0b013e3182884313] [PMID]

18. Zargaran A, Zarshenas MM, Ahmadi SA, Vessal K. Haly Abbas (949-982 AD). Journal of Neurology. 2013; 260(8):2196-7. [DOI:10.1007/s00415-012-6823-9] [PMID]

19. Zargaran A, Borhani-Haghighi A, Faridi P, Daneshamouz S, Kordafshari G, Mohagheghzadeh A. Potential effect and mechanism of action of topical chamomile (Matricaria chammomila L.) oil on migraine headache: A medical hypothesis. Med Hypotheses. 2014; 83(5):566-9. [DOI:10.1016/j.mehy.2014.08.023] [PMID]

20. Blumenthal M, Goldberg A, Brinckmann J. Herbal Medicine. Expanded Commission E Monographs. Newton: Integrative Medicine Communications; 2000. https://books.google.com/books?id=Wr9sAAAAMAAJ&q=Herbal+Medicine,+Expanded+Commission+E+Monographs&dq=Herbal+Medicine,+Expanded+Commission+E+Monographs&hl=en&sa=X&ved=2ahUKEwiqp9GU-Lv4AhVQlf0HHQd2DRoQ6AF6BAgLEAI

21. Ibn Nafis A. [Al-shamel fi Sana'at tebbi'at (Arabic)]. Abu Dhabi: Al-Majma Al-Seghafi; 2001. https://opac.nlai.ir/opac-prod/search/briefListSearch.do?command=FULL_VIEW&id=664721&pageStatus=1&sortKeyValue1=sortkey_title&sortKeyValue2=sortkey_author

22. IbnSina HBA. [Al Qanoun fe Al teb (Arabic)]. Qom: Al-Jawad Cultural Research Institute; 1013-1024. https://opac.nlai.ir/opac-prod/search/briefListSearch.do?command=FULL_VIEW&id=7984893&pageStatus=0&sortKeyValue1=&sortKeyValue2=

23. Jorjani EH. Zakhireh Kharazmshahi. Qom: Al-Jawad Cultural Research Institute; 1883. https://opac.nlai.ir/opac-prod/search/briefListSearch.do?command=FULL_VIEW&id=8387289&pageStatus=0&sortKeyValue1=&sortKeyValue2=

24. Kajla P, Sharma A, Sood DR. Flaxseed-a potential functional food source. Journal of Food Science and Technology. 2015; 52(4):1857-71. [DOI:10.1007/s13197-014-1293-y] [PMID] [PMCID]

25. Singh KK, Mridula D, Rehal J, Barnwal P. Flaxseed: A potential source of food, feed and fiber. Critical Reviews in Food Science and Nutrition. 2011; 51(3):210-22. [DOI:10.1080/10408390903537241] [PMID]

26. Singh KK, Jhamb SA, Kumar R. Effect of pretreatments on performance of screw pressing for flaxseed. Journal of Food Process Engineering. 2012; 35(4):543-56. [DOI:10.1111/j.1745-4530.2010.00606.x]

27. Tolkachev ON, Zhuchenko AA. Biologically active substances of flax: Medicinal and nutritional properties (A Review). Pharmaceutical Chemistry Journal. 2004; 34:360-7. [DOI:10.1023/A:1005217407453]

28. Oomah BD. Flaxseed as a functional food source. Journal of the Science of Food and Agriculture. 2001; 81(9):889-94. [DOI:10.1002/jsfa.898]

29. Shim YY, Gui B, Arnison PG, Wang Y, Reaney MJT. Flaxseed (Linum usitatissimum L.) bioactive compounds and peptide

nomenclature: A review. Trends in Food Science & Technology. 2014; 38(1):5-20. [DOI:10.1016/j.tifs.2014.03.011]

30. Kaithwas G, Mukherjee A, Chaurasia AK, Majumdar DK. Anti-inflammatory, analgesic and antipyretic activities of Linum usitatissimum L. (flaxseed/linseed) fixed oil.Indian Journal of Experimental Biology. 2011; 49(12):932-8. [PMID]

31. Ren GY, Chen CY, Chen GC, Chen WG, Pan A, Pan CW, et al. Effect of flaxseed intervention on inflammatory marker c-reactive protein: A systematic review and meta-analysis of randomized controlled trials. Nutrients. 2016; 8(3):136. [DOI:10.3390/nu8030136] [PMID] [PMCID]

32. Hashempur MH, Homayouni K, Ashraf A, Salehi A, Taghizadeh M, Heydari M. Effect of linum usitatissimum L. (linseed) oil on mild and moderate carpal tunnel syndrome: A randomized, double-blind, placebo-controlled clinical trial. DARU Journal of Pharmaceutical Sciences. 2014; 22(1):43. [DOI:10.1186/2008-2231-22-43] [PMID] [PMCID]

33. Chytilová M, Mudroňová D, Nemcová R, Gancarčíková S, Buleca V, Koščová J, et al. Anti-inflammatory and immunoregulatory effects of flax-seed oil and lactobacillus plantarum-biocenol™ LP96 in gnotobiotic pigs challenged with enterotoxigenic escherichia coli. Research in Veterinary Science. 2013; 95(1):103-9. [DOI:10.1016/j.rvsc.2013.02.002] [PMID]

34. Abdelkarem H, Fadda L. Flaxseed and quercetin improve anti-inflammatory cytokine level and insulin sensitivity in animal model of metabolic syndrome, the fructose-fed rats. Arabian Journal of Chemistry. 2017; 10(2):S3015-20. [DOI:10.1016/j.arabjc.2013.11.042]

35. Kalinski P. Regulation of immune responses by prostaglandin E_2. Journal of Immunology. 2012; 188(1):21-8. [DOI:10.4049/jimmunol.1101029] [PMID] [PMCID]

36. Dupasquier CM, Weber AM, Ander BP, Rampersad PP, Steigerwald S, Wigle JT, et al. Effects of dietary flaxseed on vascular contractile function and atherosclerosis during prolonged hypercholesterolemia in rabbits. American Journal of Physiology-Heart and Circulatory Physiology. 2006; 291(6):H2987-96. [DOI:10.1152/ajpheart.01179.2005] [PMID]

37. Dupasquier CM, Dibrov E, Kneesh AL, Cheung PK, Lee KG, Alexander HK, et al. Dietary flaxseed inhibits atherosclerosis in the LDL receptor-deficient mouse in part through antiproliferative and anti-inflammatory actions. American Journal of Physiology-Heart and Circulatory Physiology. 2007; 293(4):H2394-402. [DOI:10.1152/ajpheart.01104.2006] [PMID]

38. Bassett CM, McCullough RS, Edel AL, Patenaude A, LaVallee RK, Pierce GN. The α-linolenic acid content of flaxseed can prevent the atherogenic effects of dietary trans fat. American Journal of Physiology-Heart and Circulatory Physiology. 2011; 301(6):H2220-6. [DOI:10.1152/ajpheart.00958.2010] [PMID]

39. Soltanian N, Janghorbani M. A randomized trial of the effects of flaxseed to manage constipation, weight, glycemia, and lipids in constipated patients with type 2 diabetes. Nutrition & Metabolism. 2018; 15:36. [DOI:10.1186/s12986-018-0273-z] [PMID] [PMCID]

40. Mani UV, Mani I, Biswas M, Kumar SN. An open-label study on the effect of flax seed powder (Linum usitatissimum) supplementation in the management of diabetes mellitus. Journal of Dietary Supplements. 2011; 8(3):257-65. [DOI:10.3109/19390211.2011.593615] [PMID]

41. Pulkrabek M, Rhee Y, Gibbs P, Hall C. Flaxseed- and buckwheat-supplemented diets altered enterobacteriaceae diversity and prevalence in the cecum and feces of obese mice. Journal of Dietary Supplements. 2017; 14(6):667-78. [DOI:10.1080/19390211.2017.1305477] [PMID]

42. Power KA, Lepp D, Zarepoor L, Monk JM, Wu W, Tsao R, et al. Dietary flaxseed modulates the colonic microenvironment in healthy C57Bl/6 male mice which may alter susceptibility to gut-associated diseases. The Journal of Nutritional Biochemistry. 2016; 28:61-9. [DOI:10.1016/j.jnutbio.2015.09.028] [PMID]

43. Mason JK, Thompson LU. Flaxseed and its lignan and oil components: Can they play a role in reducing the risk of and improving the treatment of breast cancer? Applied Physiology, Nutrition, and Metabolism. 2014; 39(6):663-78. [DOI:10.1139/apnm-2013-0420] [PMID]

44. Flower G, Fritz H, Balneaves LG, Verma S, Skidmore B, Fernandes R, et al. Flax and breast cancer: A systematic review. Integrative Cancer Therapies. 2014; 13(3):181-92. [DOI:10.1177/1534735413502076] [PMID]

45. Al-Okbi SY. Highlights on functional foods, with special reference to flaxseed. Journal of Natural Fibers. 2005; 19(3):63-8. [DOI:10.1300/J395v02n03_06]

46. Parikh M, Maddaford TG, Austria JA, Aliani M, Netticadan T, Pierce GN. Dietary flaxseed as a strategy for improving human health. Nutrients. 2019; 11(5):1171. [DOI:10.3390/nu11051171] [PMID] [PMCID]

47. Riediger ND, Othman R, Fitz E, Pierce GN, Suh M, Moghadasian MH. Low n-6:n-3 fatty acid ratio, with fish- or flaxseed oil, in a high fat diet improves plasma lipids and beneficially alters tissue fatty acid composition in mice. European Journal of Nutrition. 2008; 47(3):153-60. [DOI:10.1007/s00394-008-0709-8] [PMID]

48. Kajla P, Sharma A, Sood DR. Flaxseed-a potential functional food source. Journal of Food Science and Technology. 2015; 52(4):1857-71. [DOI:10.1007/s13197-014-1293-y] [PMID] [PMCID]

49. Brahe LK, Le Chatelier E, Prifti E, Pons N, Kennedy S, Blædel T, et al. Dietary modulation of the gut microbiota--a randomised controlled trial in obese postmenopausal women. The British Journal of Nutrition. 2015; 114(3):406-17. [DOI:10.1017/S0007114515001786] [PMID] [PMCID]

50. Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HGM, et al. Nutrition in patients with cystic fibrosis: A European Consensus. Journal of Cystic Fibrosis .2002; 1(2):51-75. [DOI:10.1016/S1569-1993(02)00032-2]

51. Mimoun M, Coste TC, Lebacq J, Lebecque P, Wallemacq P, Leal T, et al. Increased tissue arachidonic acid and reduced linoleic acid in a mouse model of cystic fibrosis are reversed by supplemental glycerophospholipids enriched in docosahexaenoic acid. The Journal of Nutrition. 2009; 139(12):2358-64. [DOI:10.3945/jn.109.110999] [PMID]

52. Vij N. Linoleic acid supplement in cystic fibrosis: Friend or foe? American Journal of Physiology. Lung Cellular and Molecular Physiology. 2010; 299(5):L597-L8. [DOI:10.1152/ajplung.00257.2010] [PMID] [PMCID]

53. Oliver C, Watson H. Omega-3 fatty acids for cystic fibrosis. Cochrane Database of Systematic Reviews. 2016; 2016(1):CD002201. [DOI:10.1002/14651858.CD002201.pub5] [PMID] [PMCID]

54. Dijk FN, McKay K, Barzi F, Gaskin KJ, Fitzgerald DA. Improved survival in cystic fibrosis patients diagnosed by newborn screening compared to a historical cohort from the same centre. Archives of Disease in Childhood. 2011; 96(12):1118-23. [DOI:10.1136/archdischild-2011-300449] [PMID]

55. Salvatore D, Buzzetti R, Baldo E, Forneris MP, Lucidi V, Manunza D, et al. An overview of international literature from cystic fibrosis registries 2. Neonatal screening and nutrition/growth. Journal of Cystic Fibrosis. 2010; 9(2):75-83. [DOI:10.1016/j.jcf.2009.11.002] [PMID]

56. Farrell PM, Lai HJ, Li Z, Kosorok MR, Laxova A, Green CG, et al. Evidence on improved outcomes with early diagnosis of cystic fibrosis through neonatal screening: Enough is enough! The Journal of Pediatrics. 2005; 147(3):S30-6. [DOI:10.1016/j.jpeds.2005.08.012] [PMID]

57. Gostin A-I, Waisundara VY. Edible flowers as functional food: A review on artichoke (Cynara cardunculus L.). Trends in Food Science & Technology. 2019; 86:381-91. [DOI:10.1016/j.tifs.2019.02.015]

58. Alkandari D, Sarfraz H, Sidhu JS. Development of a functional food (pan bread) using amla fruit powder. Journal of Food Science and Technology. 2019; 56(4):2287-95. [DOI:10.1007/s13197-019-03718-5] [PMID] [PMCID]

59. Milner JA. Functional foods: The US perspective. The American Journal of Clinical Nutrition. 2000; 71(6):1654S-9S. [DOI:10.1093/ajcn/71.6.1654S] [PMID]

60. Hasler CM. Functional foods: Benefits, concerns and challenges-a position paper from the american council on science and health. The Journal of Nutrition. 2002; 132(12): 3772-81. [DOI:10.1093/jn/132.12.3772] [PMID]

61. Krajmalnik-Brown R, Ilhan ZE, Kang DW, DiBaise JK. Effects of gut microbes on nutrient absorption and energy regulation. Nutrition in Clinical Practice. 2012; 27(2):201-14. [DOI:10.1177/0884533611436116] [PMID] [PMCID]

62. Enaud R, Hooks KB, Barre A, Barnetche T, Hubert C, Massot M, et al. Intestinal inflammation in children with cystic fibrosis is associated with crohn's-like microbiota disturbances. Journal of Clinical Medicine. 2019; 8(5):645. [DOI:10.3390/jcm8050645] [PMID] [PMCID]

63. Ndou SP, Tun HM, Kiarie E, Walsh MC, Khafipour E, Nyachoti CM. Dietary supplementation with flaxseed meal and oat hulls modulates intestinal histomorphometric characteristics, digesta- and mucosa-associated microbiota in pigs. Scientific Reports. 2018; 8(1):5880. [DOI:10.1038/s41598-018-24043-5] [PMID] [PMCID]

64. Millman J, Okamoto S, Kimura A, Uema T, Higa M, Yonamine M, et al. Metabolically and immunologically beneficial impact of extra virgin olive and flaxseed oils on composition of gut microbiota in mice. European Journal of Nutrition. 2020; 59(6):2411-25. [DOI:10.1007/s00394-019-02088-0] [PMID] [PMCID]

65. Palla AH, Gilani A-u-H, Bashir S, Ur Rehman N. Multiple mechanisms of flaxseed: Effectiveness in inflammatory bowel disease. Evidence-Based Complementary and Alternative Medicine. 2020; 2020:7974835. [DOI:10.1155/2020/7974835] [PMID] [PMCID]

66. Simopoulos AP. Essential fatty acids in health and chronic disease. The American Journal of Clinical Nutrition. 1999; 70(3):560s-9s. [DOI:10.1093/ajcn/70.3.560s] [PMID]

67. Erdinest N, Shmueli O, Grossman Y, Ovadia H, Solomon A. Anti-inflammatory effects of alpha linolenic acid on human corneal epithelial cells. Investigative Ophthalmology & Visual Science. 2012; 53(8):4396-406. [DOI:10.1167/iovs.12-9724] [PMID]