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Possible Effect and Mechanism of Action of Flaxseed on Cystic Fibrosis Pulmonary Disorder: a Medical Hypothesis

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Abstract

Background: Cystic fibrosis (CF) as is an inherited disorder that can result in early death. Today, for treating the pulmonary symptoms of CF-related infections and inflammations, antibiotics and anti-inflammatory drugs are widely used. However, this therapeutic approach treats the symptoms without affecting the underlying causes of the disease. Thus, the present article hypothesizes the possible mechanism of action of Flaxseed as a new complementary medication for cystic fibrosis pulmonary disorder.

Material and Methods: In this hypothesis, we searched ITM textbooks such as Qanoon fi al-teb, Zakhire-Kharazmshahi, and Exir-Azam. Then, data sources including (Pub Med and Google Scholar) without time restriction from inception up to September 2020 were searched, thoroughly, for the probable mechanisms of action of this herbal medicine on CF.

Results: Flaxseed probably possesses effects for cystic fibrosis, because of the following properties: Flaxseed is rich in alpha-linolenic acid that is the omega-3 fatty acid source in the vegetarian diets, and Flaxseed has anti-inflammatory effect and also contains the flavonoid compounds which affect cystic fibrosis transmembrane conductance regulator; in addition, Flaxseed has phenolic acids (ferulic acid) which affect Pseudomonas aeruginosa by having anti-Quorum sensing (QS) activities.

Conclusion: Considering the mechanism of action of Flaxseed, the present study hypothesized that it can be used as a complementary medicine in the treatment of cystic fibrosis.

Key Words: Cystic fibrosis, Flaxseed, Iranian traditional medicine, Medicinal plants.

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1- INTRODUCTION

Cystic Fibrosis (CF) results from cystic fibrosis transmembrane conductance regulator (CFTR) mutation found in epithelial cells of those organs adjusted to the transepithelial transport of salt and water. It is also the most common deadly disease in Caucasian populations (1). CF prevalence is 1 in every 2000 to 3000 live births (2). CF may cause severe complications in different organs- i-e., azoospermia in males, intestinal blockage, and defective exocrine pancreatic function, due to dysfunction of CFTR protein and its shortage in the patients (1, 3). CFTR dysfunction leads in decreased transepithelial chloride secretion and an imbalance in the epithelial electrolyte and water homeostasis (4, 5). The thick and sticky mucus deposited in airway lumens forms following the improper transport of salt and water through epithelial cells of airways. Bacteria get stuck in it over time that leads to a persistent infection and inflammation in the airways. Tissue damage and fibrosis caused by chronic inflammation finally lead to pulmonary hypertension and exhaust most patients (1, 3). Though it is generally a multiorgan disorder, the major cause of morbidity and mortality in CF is the progressive pulmonary involvement (6-8), which results from infection caused by *Pseudomonas aeruginosa* (PA) and chronic pulmonary infections (9, 10).

Although there is difficulty in treating recurrent PA-related infections and other pathogens in CF patients, but different treatment strategies have been developed over the past few decades that have significantly a positive impact on the prognosis of this disease (11). Today, for treating the symptoms of CF-related infections and inflammations, antibiotics and anti-inflammatory drugs are widely used. Furthermore, bronchodilators, mucolytics, and osmotic agents are prescribed to improve the clearance of the airways and sputum (11-15). However, this therapeutic approach treats the symptoms of the disease without affecting its underlying causes (16).

The complexity of the drug regimen in the chronic diseases have led to about 50% compliance for treatments in patients (17), and in recent years, the use of traditional and complementary medicine to reduce the symptoms of CF has been considered by health care providers and about 66% of patients with CF have used one of the alternatives and complementary methods (18).

Complementary and traditional medicine develop new drugs usually origined in natural products. Iranian Traditional Medicine (ITM) is an ancient health practice with worthy roots (19, 20), which date back to thousands of years (21). Iranian Muslim physicians, like Avicenna (980–1037AD) and many others in the early medieval, played a pivotal role in its flourishment (20, 22) so that their manuscripts- e g, the Canon by Avicenna, were the medical textbook in European universities from 11th to 17th centuries (19). These manuscripts were written and used in Iran till the 18th century. The issues and medications suggested in these manuscripts written from the 10th to the 18th century benefit from an 800-year support by Iranian physicians through examinations and trials (23).

Currently, the use of complementary and Traditional medicine as a therapeutic factor for chronic diseases is being accepted in WHO strategies (24). The present hypothesis aimed at investigating an Iranian Traditional herbal medicine, Flaxseed, as the complementary treatment of CF, cited frequently by many Iranian old medical texts.

2- MATERIAL AND METHODS

In this hypothesis, in order to investigate the effects of Flaxseed on pulmonary symptoms caused by thick and

sticky airway secretions of patients with cystic fibrosis, acceptable information was extracted from ITM textbooks such as Qanoon fi al-teb, Zakhire-Kharazmshahi, and Exir-Azam. Then, data sources including (Pub Med and Google Scholar) without time restriction, from inception up to September 2020, were searched by using the combination of keywords such as (cystic fibrosis, *Pseudomonas aeruginosa*, CFTR, flavonoids, kaempferol, quercetin, inflammation, alpha-linolenic acid, omega 3, ferulic acid, anti-quorum sensing (QS) activity, the type III secretion systems (TTSS)) and Flaxseed were searched thoroughly for the probable mechanisms of action of this herbal medicine "Flaxseed" on CF; in addition, the present study hypothesized that it is a new drug developed based on the suggested formula.

3- RESULTS

In this hypothesis, we attempted to introduce the potential effects of Flaxseed on CFTR, *Pseudomonas aeruginosa* and pulmonary inflammation in CF patients, described one by one in the following section.

3-1. Cystic fibrosis in Iranian Traditional Medicine

There is no cystic fibrosis disorder in Iranian Traditional Medicine (ITM) sources, but due to the production of thickened secretions in the body ducts, it is classified in the group of diseases caused by the production of thick and sticky secretions. In this assay, we have mentioned Flaxseed as a single herb, recommended in many ITM text books and some recent studies for thick and sticky airway secretions management, as well as its related effects. Flaxseed is one of the most recommended herbs for these types of diseases in ITM documents (25-27).

3-2. Flaxseed

Flax (*Linum usitassimum*) is the member of Lineaceae family (28). The Flaxseed is a medicinal herb, any part of which is used for a certain medical purpose (29, 30). The consumption of Flaxseed has an ancient history (31). Nowadays, more than 50 countries, mostly in the Northern hemisphere, cultivate this plant (32). Countries involved in the cultivation and production of flaxseed include Canada, China, United States, India and Ethiopia (33). Flaxseed is widely used in Iranian Traditional Medicine and it is cited as a treatment for thick and sticky secretions in many Iranian Traditional manuscripts (25-27). Flaxseed contains fat, protein, soluble and insoluble fiber, phenolic, trypsin inhibitor, linatine, lignans (phytoestrogens), minerals, vitamins and selenium (34). Furthermore, Flaxseed has anti-inflammatory effect (35-40). Approved pharmacological effect of flaxseed include decreasing the progression of atherosclerosis (41-43), reducing blood glucose in type 2 diabetic patients (44, 45), alterating the bacterial flora in the animals intestines (46, 47) and having anti-cancer effects (48, 49).

3-2-1. Expected mechanisms of action of Flaxseed in cystic fibrosis pulmonary disorder

According to the main theories regarding CF, it seems that Flaxseed can be suggested as a novel drug with natural origin enjoying an advance formula for the treatment of CF, considering of the following reasons:

Flaxseed is rich in alpha-linolenic acid (ALA) (32) that is the omega-3 fatty acid source in the vegetarian diets (29, 30, 50). Also Flaxseed has anti-inflammatory effect (51-55) and possesses phenolic acids (ferulic acid) (56) which affect *Pseudomonas aeroginosa* (57) by having anti-quorum sensing (QS) activities, and also contains flavonoid compound which affects CFTR (56).

3-2-1-1. Flaxseed and CFTR

Since CFTR regulates salt and water transepithelial transportations, it exists in a variety of epithelial cells (1).

Flavonoids are categorized as a class of secondary plant metabolites having protective effects against immune and inflammatory reactions. They play a pivotal role in the growth and development of plants (56).

Biochemical analysis of the seedcake extracted from transgenic Flaxseeds demonstrated significant increase in flavonoids (kaempferol). High-performance liquid chromatography (HPLC) analysis of the methanolic extract of the seeds from W92.72 and W92.40 transgenic lines showed higher amounts of quercetin (90% and 46%, respectively); in addition, kaempferol accumulation was also observed in the lines W92.40 and W92.72 by 70% and 83%, respectively (56).

Genistein is a plant-derived isoflavone, which its biological activity was first described in 1940s and early 1950s. In 1980s, it was found that quercetin, a flavone from this group, can inhibit the activity of protein kinase C (PKC), phosphorylase kinase, casein kinase, and the tyrosine kinase associated with the Rous sarcoma virus gene product pp60src (58). Now it is evident that genistein and some related flavones and isoflvones can affect transportation of ions in epithelial cells. This finding was first reported by Nguyen et al. They indicated that quercetin and kaempferol can affect CFTR-medicated ion transport and stimulate secretion of Cl^- across T84 cells (58, 59). A study on IB3-1 (F508/W1282X) bronchial epithelial cells, for examining the effect of flavonoids on CFTR, showed that apigenin, genistein, kaempferol, and quercetin (1 or 5 µmol) can alter the immunofluorescence distribution. Intracellular CFTR was demonstrated during 24-hour treatment with apigenin, genistein, and kaempferol. Finally, this study found combination therapy with selective flavonoids to be useful in the treatment of cystic fibrosis (60). One study showed that flavonoid Quercetin stimulates CFTR in respiratory epithelial in vivo and in vitro (6). Another study showed that an extract from the *Phyllanthus acidus* (medicinal plant) and its isolated compounds, like kaempferol, provoke airway chloride secretion by activating CFTR (32).

3-2-1-2. Flaxseed and inflammation

CF patients' airways are normal at birth except for the plugged and dilated submucosal gland ducts, which indicate prenatal changes in the airways. Pulmonary diseases start in childhood. Newborns who are diagnosed by newborn screening, following diagnosis showed inflammation and infection with bacteria, particularly with *Staphylococcus aureus*. Broncho alveolar lavage fluid at high levels was found with inflammatory markers, like interleukin 8 (IL-8), peroxidases, and their oxidants, even among newborns with normal lung function and with no evident bacterial colonization (61, 62). One study revealed that dietary Flaxseed reduced lung inflammation and lipid peroxidation that indicate protective effect upon pro-oxidant-related tissue destruction in vivo (63). There are some studies that show the anti-inflammatory effect of flaxseed and Alpha-linolenic acid, some of which are reported in the following: A study found that flaxseed had significant effects on reducing C - reactive protein in obese people (64). Another study found that the combined use of *L. Plantarum* probiotics with flaxseed-rich flakes of n-3 PUFAs had anti-inflammatory effects by stimulating immune cells associated with Th1 and phagocytosis (65). Yet another study found that flaxseed and quercetin improved the levels of anti-inflammatory

cytokines (66). A further study showed that concentration of IL-6, IL-1Beta and TNF-alpha produced by peripheral blood mononuclear cells and serum TNF-alpha were lower in ALA diet than in the other studied diets (67). The only study on CF and Flaxseed revealed that Flaxseed modulates inflammatory oxidative stress biomarkers and inflammation in cystic fibrosis (68).

3-2-1-3. Flaxseed and *Pseudomonas aeruginosa*

Infection is the leading cause of morbidity and mortality in these patients due to *Pseudomonas aeruginosa* and chronic respiratory infections (9, 69). To react, lung infections with organisms, like *P. aeruginosa* and neutrophils (white blood cells) accumulate in the airways, producing proteolytic enzymes and oxidants that intercede the inflammatory reaction (70, 71). The thick and viscous secretions are caused by such neutrophils leading to mucus plugs in the smaller airways and consequently infection and inflammation. Treating with anti-inflammatory agents, such as corticosteroids (71, 72) and non-steroidal anti-inflammatory agents (71, 73) is effective (71).

In addition, *P. aeruginosa* is the human opportunistic pathogen, which prefers to infect cystic fibrosis patients. The pathogen generates many extracellular productions such as pyocyanin (74, 75). Such extracellular virulence factors seem essential in competing *Pseudomonas aeruginosa* for establishing and maintaining infection. Their production is managed by quorum sensing system (QS). *Pseudomonas aeruginosa* also engages QS to control the organization of biofilms (74, 76). Biofilm generation can protect the microorganisms against host defenses and supply elevated resistance against antibacterial agents (74, 77). Inactivation of the QS system in a pathogen had significantly decreased virulence factor generation (74, 78).

The main mechanism that lets *P. aeruginosa* to increase in affected hosts and overcome host defense strategies is secreting different protein factors by specific secretion apparatus. The *Pseudomonas aeruginosa* genome can harbor genes for the type II and III secretion systems (TTSS) (79). The latter is a specific cytotoxin-translocating apparatus including gram-negative bacteria related to septic shock, lung injury, and inappropriate patient outcomes (80). Although *Pseudomonas aeruginosa* TTSS genes are available in almost all environmental and clinical isolates (81), TTSS expression is linked to more serious infections (82). The TTSS-expressing phenotype rate in 108 clinical isolates of *P. aeruginosa* was remarkably more in acutely infected cases in comparison to CF patients with chronic infection; and it was associated with a higher mortality rate (83).

Plants as promising sources of molecules inhibiting bacterial QS have been long applied in medicine (57, 84, 85). Flaxseed has Phenolic compounds (56) that are the plants' secondary metabolites, extensively found in plant kingdom with antioxidant and antimicrobial effects (57, 86). Nonetheless, their anti-QS effects on microorganisms have been not widely considered (57). Biochemical analysis of the seeds' extracts of transgenic flax plants showed a significant elevation in the levels of phenolic acids (coumaric, ferulic, and synapic acids) (56). Additionally, one study showed that flaxseed oil has antibiofilm activity against methicillin-sensitive S. aureus, Methicillin-resistant *S. aureus*, *Klebsiella pneumonia* and *Staphylococcus epidermidis* (87), and another study showed that flaxseed extract has positive antibacterial effects against *Streptococcus mutans, Streptococcus pyogenes, Pseudomona aerigenosa;* and it

was comparable in efficacy to that of Streptomycin (88).

3-2-1-4. Flaxseed and omega 3

ALA and linoleic acid (LA) are two fatty acids, respectively, belonging to the omega-3 and omega-6 families of polyunsaturated fatty acids (PUFAs), which are essential for humans and should be obtained from food. During the PUFAs metabolism, long chain fatty acids are derived that have significant biological activities (89).

Omega-3 fatty acids, by applying anti-inflammatory responses, play a pivotal role in the cell membrane integrity. Regarding their effect on inflammatory complications, omega-3 fatty acids can reduce the conversion of the omega-6 fatty acids to pro-inflammatory metabolites and increase the production of those omega-3 end products that are biologically less-active (90). ALA is converted to docosahexaenoic (DHA) and eicosapentaenoic (EPA) acids, and LA to arachidonic acid (AA). No mechanism has been recognized thus far for the low levels of LA in CF; however, a potential mechanism can be the elevated metabolism of the omega-6 fatty acids (89).

Some factors in patients with CF disrupt fatty acids uptake (90) and accordingly, compared to healthy people, the serum essential fatty acids are in lower levels in such patients (89). Therefore, although achieving a certain therapeutic regimen needs further investigations, omega-3 fatty acids supplementation can be a treatment of choice in patients with CF (90). The clinical benefits and feasibility of omega-3 fatty acids supplementation in CF are investigated in about 10 studies. DHA, an omega-3 fatty acid, can normalize LA metabolism, according to recent data; and so, it can help scientists to provide a rationale supplementation regimen (89).

According to recent findings, changes in serum fatty acid concentration contribute to the pathogenesis in lungs. For instance, serum essential fatty acid levels are usually lower in patients with CF than in healthy people. The infection caused by *Pseudomonas aeruginosa* plays a crucial role in the pathogenesis of CF, although the reason for the vulnerability of CF patients to these bacteria is unclear yet. As already known, by targeting sphingolipid metabolism and ceramide accumulation, omega-3 PUFAs containing bioactive compounds (like DHA ethyl ester) can modulate inflammation and immune responses in CF and chronic inflammatory diseases; hence, they can be suggested as alternatives to supplementation with high-dose LA. It is already known that the expression of a CFTR gene encountered mutations alters the metabolism of sphingolipids and ceramic accumulation that affects the vulnerability of the patient with CF to infections and inflammations. Evidently, the lack of a wild-type CFTR expression intensifies the accumulation of ceramide. Data obtained from studies on mouse models of CF show that if ceramide levels are normalized, the secretion of inflammatory markers and accordingly, the susceptibility to infections decreases (89).

Nutritionists suggest the incorporated consumption of omega-3 fatty acid sources and Flaxseed is highly rich in omega-3 fatty acid and can be the best source of this compound for those who do not eat marine foods (29, 30). Flaxseed is the source of ALA as a functional ingredient. In the vegetarian diets, it is the exclusive omega-3 fatty acid source (29, 30, 50). ALA is a fundamental PUFA that exhibits anti-inflammatory, anti-thrombotic, and anti-arrhythmic activities (91). The amount of omega-3 fatty acids in Flaxseed oil is 6 times higher than it in fish oil (92), also Flaxseed has anti-inflammatory effects (51-55). Flaxseed oil inhibits prostaglandin E2 (PGE2) (51). PGE2 inhibits

macrophage, neutrophil, and T helper type 1 (Th1) function and enhances T helper type 2 (Th2), T helper type 17 (Th17), and T regulatory responses (93). Therefore, with this mechanism, it can be effective in modulating the immune response. The oil also inhibits arachidonic acid-induced inflammation by inhibiting the inhibitory capacity of both cyclooxygenase and lipoxygenase in arachidonic acid metabolism (51).

4- Conclusion

CF is also the most common deadly disease in Caucasian populations. Although it is generally a multi-organ disorder, but progressive respiratory involvement is a major cause of mortality and morbidity in most patients and the main cause of mortality and morbidity in these patients is infection caused by airway obstruction because of the thick and sticky secretions. Plant "Flaxseed" for the management of cystic fibrosis presented in this study is supported by classical Iranian traditional texts as well as recent investigations. According to the mentioned studies, Flaxseed is a medical herb for the respiratory diseases with high thick and sticky secretions production and all the ingredients of this herb according to this review, affect the cystic fibrosis pulmonary pathogenesis that by the glance Flaxseed is a good source of ALA, which is the omega-3 fatty acid source in the vegetarian diets. Also Flaxseed has anti-inflammatory and anti-bacterial effects and possesses phenolic acids (ferulic acid) which affects *P.aeroginosa* by having anti-QS activity, and also contains flavonoid compounds which affect CFTR. This medical herb prepares a proper complementary and alternative to conventional medications, with fewer complications. Systematic validity studies are needed to enhance the traditional drugs as complementary and alternative medications for cystic fibrosis. It seems that some of the components present in this plant can be employed for designing new drugs.

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5- REFERENCES

1. Dey I SK, Bradbury NA. Natural Compounds as Therapeutic Agents in the Treatment Cystic Fibrosis. Journal of genetic syndromes & gene therapy 2016; 7: 284. doi:10.4172/2157-7412.1000284.

2. Hamosh A FS MM, Jr., Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. J Pediatr 1998; 132: 255-9. doi:10.1016/s0022-3476(98)70441-x.

3. Riordan JR RJ KB, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989; 245: 1066-73. doi:10.1126/science.2475911.

4. Grasemann H GT AJ, Klingel M, Tullis E, Ratjen F. Effect of ivacaftor therapy on exhaled nitric oxide in patients with cystic fibrosis. J Cyst Fibros 2015; 14: 727-32. doi:10.1016/j.jcf.2015.07.001.

5. Ratjen F, Döring G. Cystic fibrosis. The Lancet 2003; 361: 681-9. doi:10.1016/s0140-6736(03)12567-6

6. Gibson RL BJ, Ramsey BW. Pathophysiology and management of

pulmonary infections in cystic fibrosis. Am J Respir Crit Care Med 2003; 168: 918-51. doi:10.1164/rccm.200304-505SO.

7. Elborn JS. Cystic fibrosis. Lancet 2016; 388: 2519-31. doi:10.1016/s0140-6736(16)00576-6

8. Ratjen F BS RS, Goss CH, Quittner AL, Bush A. Cystic fibrosis. Nat Rev Dis Primers 2015; 1: 15010. doi:10.1038/nrdp.2015.10.

9. Alhazmi A. Pseudomonas aeruginosa – Pathogenesis and Pathogenic Mechanisms. International Journal of Biology 2015; 7. doi:10.5539/ijb.v7n2p44

10. Yu H HM CC, Boucher JC, Deretic V. Microbial pathogenesis in cystic fibrosis: pulmonary clearance of mucoid Pseudomonas aeruginosa and inflammation in a mouse model of repeated respiratory challenge. Infect Immun 1998; 66: 280-8. doi:10.1128/iai.66.1.280-288.1998.

11. Velino C, Carella F, Adamiano A, Sanguinetti M, Vitali A, Catalucci D, et al. Nanomedicine Approaches for the Pulmonary Treatment of Cystic Fibrosis. Front Bioeng Biotechnol 2019; 7: 406. doi:10.3389/fbioe.2019.00406

12. Abramowsky CR, Swinehart GL. The nephropathy of cystic fibrosis: a human model of chronic nephrotoxicity. Hum Pathol 1982; 13: 934-9. doi:10.1016/s0046-8177(82)80056-7

13. Ramsey BW. Management of pulmonary disease in patients with cystic fibrosis. N Engl J Med 1996; 335: 179-88. doi:10.1056/nejm199607183350307

14. Geller DE. Aerosol antibiotics in cystic fibrosis. Respir Care 2009; 54: 658-70. doi:10.4187/aarc0537

15. Agent P, Parrott H. Inhaled therapy in cystic fibrosis: agents, devices and regimens. Breathe (Sheff) 2015; 11: 110-8. doi:10.1183/20734735.021014

16. Savla R, Minko T. Nanotechnology approaches for inhalation treatment of fibrosis. J Drug Target 2013; 21: 914-25. doi:10.3109/1061186x.2013.829078

17. Conway SP, Pond MN, Hamnett T, Watson A. Compliance with treatment in adult patients with cystic fibrosis. Thorax 1996; 51: 29-33. doi:10.1136/thx.51.1.29

18. Stern RC, Canda ER, Doershuk CF. Use of nonmedical treatment by cystic fibrosis patients. J Adolesc Health 1992; 13: 612-5. doi:10.1016/1054-139x(92)90376-m

19. Zargaran A ZM MA, Mohagheghzadeh A. Management of tremor in medieval Persia. J Hist Neurosci 2013; 22: 53-61. doi:10.1080/0964704x.2012.670475.

20. Zargaran A ZM, Mehdizadeh A, Mohagheghzadeh A. Management of tremor in medieval Persia. J Hist Neurosci 2013; 22: 53-61. doi:10.1080/0964704x.2012.670475.

21. Zargaran A FA MASasfaP, 000 years of surgical history). World J Surg 2013; 37: 2002-4. doi:10.1007/s00268-013-2055-0.

22. Golzari SE KZ GK, Hosseinzadeh H, Soleimanpour H, Azarfarin R, et al. Contributions of Medieval Islamic physicians to the history of tracheostomy. Anesth Analg 2013; 116: 1123-32. doi:10.1213/ANE.0b013e3182884313.

23. Zargaran A B-HA FP, 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. Medical hypotheses 2014; 83: 566-9. doi:10.1016/j.mehy.2014.08.023.

24. Qi Z, Kelley E. The WHO traditional medicine strategy 2014–2023: a perspective. Science. 2014;346(6216):S5-S6.

25. IbnSina AAHiA, 2005. Al Qanoun fe Al teb Al elmy al matbouat Institute, Lebanon.

26. Jorjani SI. zakhireh Kharazmshahi (persian). 1. 1 ed. Qom: Ehya'e tibbe tabiee; pp.477

27. Azam khan M (1869). Exir Azam (Great Elixir) [in Persian]. India: Monshi Nou.

28. Kajla P SA, Sood DR. Flaxseed-a potential functional food source. Journal of food science and technology 2015; 52: 1857-71. doi:10.1007/s13197-014-1293-y.

29. Singh KK MD RJ, Barnwal P. Flaxseed: a potential source of food, feed and fiber. Crit Rev Food Sci Nutr 2011; 51: 210-22. doi:10.1080/10408390903537241.

30. SINGH KK JS, KUMAR R. EFFECT OF PRETREATMENTS ON PERFORMANCE OF SCREW PRESSING FOR FLAXSEED. Journal of Food Process Engineering 2012; 35: 543-56. doi: 10.1111 / j. 1745 -4530. 2010. 00606.x.

31. 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

32. Oomah BD. Flaxseed as a functional food source. Journal of the Science of Food and Agriculture 2001; 81: 889-94. doi:10.1002/jsfa.898

33. Goyal A, Sharma V, Upadhyay N, Gill S, Sihag M. Flax and flaxseed oil: an ancient medicine & modern functional food. J Food Sci Technol 2014; 51: 1633-53. doi:10.1007/s13197-013-1247-9

34. 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: 5-20. doi: https: // doi. Org / 10. 1016 / j.tifs.2014.03.011

35. Kaithwas G, Mukherjee A, Chaurasia AK, Majumdar DK. Anti-inflammatory, analgesic and antipyretic activities of Linum usitatissimum L. (flaxseed/linseed) fixed oil. Indian J Exp Biol 2011; 49: 932-8.

36. 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: 136. doi:10.3390/nu8030136

37. 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 2014; 22: 43. doi:10.1186/2008-2231-22-43

38. 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. Res Vet Sci 2013; 95: 103-9. doi: 10.1016 / j. rvsc. 2013.02.002

39. 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 2013; 131. doi:10.1016/j.arabjc.2013.11.042

40. Kalinski P. Regulation of immune responses by prostaglandin E2. J Immunol 2012; 188: 21-8. doi:10.4049/jimmunol.1101029

41. 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. Am J Physiol Heart Circ Physiol 2006; 291: H2987-96. doi:10.1152/ajpheart.01179.2005

42. 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. Am J Physiol Heart Circ Physiol 2007; 293: H2394-402. doi:10.1152/ajpheart.01104.2006

43. 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. Am J Physiol Heart Circ Physiol 2011; 301: H2220-6. doi:10.1152/ajpheart.00958.2010

44. 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. Nutr Metab (Lond) 2018; 15: 36. doi:10.1186/s12986-018-0273-z

45. 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. J Diet Suppl 2011; 8: 257-65. doi:10.3109/19390211.2011.593615

46. 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. J Diet Suppl 2017; 14: 667-78. doi:10.1080/19390211.2017.1305477

47. 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. J Nutr Biochem 2016; 28: 61-9. doi:10.1016/j.jnutbio.2015.09.028

48. 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? Appl Physiol Nutr Metab 2014; 39: 663-78. doi:10.1139/apnm-2013-0420

49. Flower G, Fritz H, Balneaves LG, Verma S, Skidmore B, Fernandes R, et al. Flax and Breast Cancer: A Systematic Review. Integr Cancer Ther 2014; 13: 181-92. doi:10.1177/1534735413502076

50. Riediger ND OR FE, 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. Eur J Nutr 2008; 47: 153-60. doi:10.1007/s00394-008-0709-8.

51. Kaithwas G MA CA, Majumdar DK. Anti-inflammatory, analgesic and antipyretic activities of Linum usitatissimum L. (flaxseed/linseed) fixed oil. Indian J Exp Biol 2011; 49: 932-8.

52. Ren GY CC CG, 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: 136. doi:10.3390/nu8030136.

53. Hashempur MH HK AA, 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 2014; 22: 43. doi:10.1186/2008-2231-22-43.

54. Chytilová M MD NR, 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. Res Vet Sci 2013; 95: 103-9. doi:10.1016/j .rvsc.2013.02.002. .

55. Abdelkarem H FLFaqia-iclaisiamoms, the fructose-fed rats. Arabian Journal of Chemistry 2013; 131. doi:10.1016/j.arabjc.2013.11.042.

56. Zuk M KA DL, Szołtysek K, Prescha A, Hanuza J, et al. Flavonoid engineering of flax potentiate its biotechnological application. BMC Biotechnol 2011; 11: 10. doi:10.1186/1472-6750-11-10.

57. Ugurlu A KYA US, Aksu B, Bosgelmez-Tinaz G. Phenolic compounds affect production of pyocyanin, swarming motility and biofilm formation of Pseudomonas aeruginosa. Asian Pacific Journal of Tropical Biomedicine 2016; 6: 698-701. doi:10.1016/j.apjtb.2016.06.008.

58. SCHULTZ BD SA DD, BRIDGES RJ. Pharmacology of CFTR Chloride Channel Activity. Physiological Reviews 1999; 79: S109-S44. doi:10.1152/physrev.1999.79.1.S109. .

59. Nguyen TD CA HG, Gettys TW, Cohn JA. Stimulation of secretion by the T84 colonic epithelial cell line with dietary flavonols. Biochemical pharmacology 1991; 41: 1879-86. doi:10.1016/0006-2952(91)90127-q.

60. Lim M MK FA, Kwon E, Zeitlin P. Modulation of ΔF508 Cystic Fibrosis Transmembrane Regulator Trafficking and Function with 4-Phenylbutyrate and Flavonoids. American journal of respiratory cell and molecular biology 2004; 31: 351-7. doi:10.1165/rcmb.2002-0086OC. .

61. Ranganathan SC PF, Gangell C, Brennan S, Stick SM, Sly PD. Evolution of pulmonary inflammation and nutritional status in infants and young children with cystic fibrosis. Thorax 2011; 66: 408-13. doi:10.1136/thx.2010.139493.

62. Cohen-Cymberknoh M KE, Ferkol T, Elizur A. Airway inflammation in cystic fibrosis: molecular mechanisms and clinical implications. Thorax 2013; 68: 1157-62. doi:10.1136/thoraxjnl-2013-203204.

63. Kinniry P AY, Vachani A, Solomides CC, Arguiri E, Workman A, et al. Dietary flaxseed supplementation ameliorates inflammation and oxidative tissue damage in experimental models of acute lung injury in mice. J Nutr 2006; 136: 1545-51. doi:10.1093/jn/136.6.1545.

64. Ren GY CC, 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: 136. doi:10.3390/nu8030136.

65. Chytilová M MD, 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. Res Vet Sci 2013; 95: 103-9. doi:10.1016/j.rvsc.2013.02.002.

66. Abdelkarem HM FLFaqia-iclaisiamoms, the fructose-fed rats. Arabian Journal of Chemistry 2017; 10: S3015-S20. doi:https://doi.org/10.1016/j.arabjc.2013.11.042.

67. Zhao G ET, Martin KR, Gillies PJ, West SG, Kris-Etherton PM. Dietary alpha-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. Am J Clin Nutr 2007; 85: 385-91. doi:10.1093/ajcn/85.2.385.

68. Turowski JB PR, Lawson JA, Christofidou-Solomidou M, Hadjiliadis D. Flaxseed modulates inflammatory and

oxidative stress biomarkers in cystic fibrosis: a pilot study. BMC Complement Altern Med 2015; 15: 148. doi:10.1186/s12906-015-0651-2.

69. Yu H HM, Chrisp CE, Boucher JC, Deretic V. Microbial pathogenesis in cystic fibrosis: pulmonary clearance of mucoid Pseudomonas aeruginosa and inflammation in a mouse model of repeated respiratory challenge. Infection and immunity 1998; 66: 280-8. doi:10.1128/IAI.66.1.280-288.1998.

70. Wilmott RW K-HG, Stark JM. Current concepts on pulmonary host defense mechanisms in children. Curr Opin Pediatr 2000; 12: 187-93. doi:10.1097/00008480-200006000-00002.

71. Oliver C, Jahnke N. Omega-3 fatty acids for cystic fibrosis. Cochrane Database Syst Rev 2011; Cd002201. doi:10.1002/14651858.CD002201.pub3

72. Cheng K AD, Smyth R. Oral steroids for cystic fibrosis. Cochrane Database Syst Rev 2000; Cd000407. doi:10.1002/14651858.Cd000407.

73. Lands LC, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis. Cochrane Database Syst Rev 2007; Cd001505. doi:10.1002/14651858.CD001505.pub2

74. Ugurlu A KYA, Ulusoy S, Aksu B, Bosgelmez-Tinaz G. Phenolic compounds affect production of pyocyanin, swarming motility and biofilm formation of Pseudomonas aeruginosa. Asian Pacific Journal of Tropical Biomedicine 2016; 6: 698-701. doi:https://doi.org/10.1016/j.apjtb.2016.06.008.

75. Girard G, Bloemberg GV. Central role of quorum sensing in regulating the production of pathogenicity factors in Pseudomonas aeruginosa. Future Microbiol 2008; 3: 97-106. doi:10.2217/17460913.3.1.97

76. Haussler S, Fuqua C. Biofilms 2012: new discoveries and significant wrinkles in a dynamic field. J Bacteriol 2013; 195: 2947-58. doi:10.1128/jb.00239-13

77. Høiby N BT, Givskov M, Molin S, Ciofu O. Antibiotic resistance of bacterial biofilms. Int J Antimicrob Agents 2010; 35: 322-32. doi:10.1016/j.ijantimicag.2009.12.011.

78. Jakobsen TH vGM, Christensen LD, Bjarnsholt T, Givskov M. Qualitative and quantitative determination of quorum sensing inhibition in vitro. Methods Mol Biol 2011; 692: 253-63. doi:10.1007/978-1-60761-971-0_18.

79. Lee VT SR, Tümmler B, Lory S. Activities of Pseudomonas aeruginosa effectors secreted by the Type III secretion system in vitro and during infection. Infect Immun 2005; 73: 1695-705. doi:10.1128/iai.73.3.1695-1705.2005.

80. Ader F LBR, Faure K, Gosset P, Epaulard O, Toussaint B, et al. Alveolar response to Pseudomonas aeruginosa: role of the type III secretion system. Infect Immun 2005; 73: 4263-71. doi:10.1128/iai.73.7.4263-4271.2005.

81. Feltman H SG, Khan S, Jain M, Peterson L, Hauser AR. Prevalence of type III secretion genes in clinical and environmental isolates of Pseudomonas aeruginosa. Microbiology (Reading) 2001; 147: 2659-69. doi:10.1099/00221287-147-10-2659.

82. Sawa T OM, Kurahashi K, Twining SS, Frank DW, Doroques DB, et al. In vitro cellular toxicity predicts Pseudomonas aeruginosa virulence in lung infections. Infection and immunity 1998; 66: 3242-9. doi:10.1128/iai.66.7.3242-3249.1998.

83. Roy-Burman A SR, Racine S, Swanson BL, Revadigar NS, Fujimoto J, et al. Type III protein secretion is associated with death in lower respiratory and systemic Pseudomonas aeruginosa

infections. J Infect Dis 2001; 183: 1767-74. doi:10.1086/320737.

84. González-Lamothe R MG, Gattuso M, Diarra MS, Malouin F, Bouarab K. Plant antimicrobial agents and their effects on plant and human pathogens. Int J Mol Sci 2009; 10: 3400-19. doi:10.3390/ ijms 10083400.

85. Nazzaro F FF, Coppola R. Quorum sensing and phytochemicals. Int J Mol Sci 2013; 14: 12607-19. doi:10.3390/ijms 140612607.

86. Del Rio D R-MA, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid Redox Signal 2013; 18: 1818-92. doi:10.1089/ars.2012.4581.

87. Harith Jabbar Fahad Al-Mathkhury* ASA-DK-T. Antibacterial and Antibiofilm Activity of Flaxseed Oil. . Iraqi Journal of Science 2016; 57.

88. Basma Ezzat Mustafa Alahmad MAK PK, L Subramaniam, Khairani Idah Binti Mokhtar, Nazih shaban Mustafa, Omar Abdul, Jabbar Abdul Qader, Nur Dalila Binti Zolkofli, Wan Nor Syahirah Binti Wan. The antibacterial effect of flaxseed extract on selective oral pathogens-comparative in vitro study. . World journal of pharmacy and pharmaceutical sciences 2018; 7. doi:10.20959/wjpps201811-12548.

89. Vij N. Linoleic acid supplement in cystic fibrosis: friend or foe? American journal of physiology Lung cellular and molecular physiology 2010; 299: L597-L8. doi:10.1152/ajplung.00257.2010

90. Oliver C, Watson H. Omega-3 fatty acids for cystic fibrosis. Cochrane Database Syst Rev 2016; 2016: Cd002201. doi:10.1002/14651858.CD002201.pub5

91. Simopoulos AP. Essential fatty acids in health and chronic disease. Am J Clin Nutr 1999; 70: 560s-9s. doi:10.1093/ajcn /70.3. 560s

92. Asif M. Health effects of omega-3, 9 fatty acids: Perilla frutescens is a good example of plant oils. Oriental pharmacy and experimental medicine 2011; 11: 51-9. doi:10.1007/s13596-011-0002-x.

93. Kalinski P. Regulation of immune responses by prostaglandin E2. J Immunol 2012; 188: 21-8. doi:10.4049/jimmunol. 1101029